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Endocrinology

The Bulletin *of the*
Association *for the* Study *of*
Internal Secretions

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This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators, in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

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Manuscripts of three types of original work are desired for publication:

a. *Clinical studies* of endocrine diseases and the part played by the endocrine organs as contributing factors in other diseases;

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Manuscripts may be submitted in any modern language, and if found suitable for publication will be translated into English without expense to the authors. To insure a version, however, satisfactory to the author, it is desirable that the article be submitted, when feasible, in English.

Readers who encounter articles of endocrine interest in unusual periodicals or under captions not indicating such interest are requested to submit abstracts for publication.

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Correspondence relating to advertising and business matters should be addressed to Endocrinology, 1045-6-7 Rowan Bldg., Los Angeles, California.

THE TWELFTH ANNUAL MEETING

The Twelfth Annual meeting of The Association for the Study of Internal Secretions will be held in the Loring Theater, Minneapolis, Minn., Tuesday, June 12, 1928, with two sessions, 9 A.M. and 2 P.M.

The Loring Theater is located on Nicollet Avenue, between 14th and 15th Streets. This is about two and a half blocks from the Municipal Auditorium, which will be the headquarters of the American Medical Association.

The following program has been arranged and will be presented as indicated:

9 A.M.

The Relationship of Iodine to Thyroid Hypoplasia and Function.
J. Earl Else, Portland, Oregon

Iodine Deficiency Symptoms and their Significance in Animal Nutrition and Pathology.
John M. Evvard, Ames, Iowa

The Clinical Differentiation of Exophthalmic Goiter and Hyperfunctioning Adenomatous Goiter.
H. S. Plummer, Rochester, Minn.

The Relations of Infections to Goiter.
Warren H. Cole, St. Louis

Congenital Goiter: Report of a Case Occurring after the Administration of Potassium Iodide to Mother during Pregnancy.
David P. Seecof, Denver

Discussion on above papers opened by Frank H. Lahey, Boston

The Relation of the Internal Secretion to Calcium Metabolism. Particularly the Thyroid and Parathyroid.
Joseph C. Aub, Boston

2 P.M.

President's Address. The Uni-Glandular Origin of Pluri-Glandular Syndromes.
H. Lisser, San Francisco

Mixed Adenomas of the Pituitary.
Harvey Cushing and Percival Bailey, Boston

Hypophysectomized Puppies.
F. L. Reichert, San Francisco

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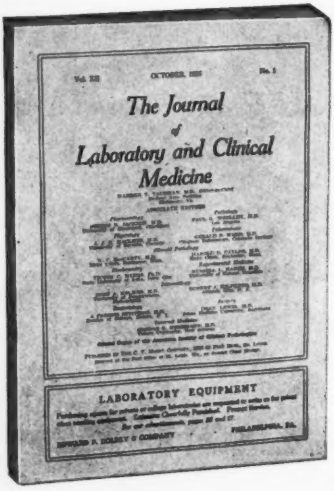

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The Influences of the Anterior Hypophysis upon the Development and Activity of the Gonads as Indicated by Its Experimental Ablation and Transplantation.

Philip E. Smith, New York

The Normal Proportions of the Different Constituents of the Human Hypophysis. (Statistical Study of about 200 Organs.)

A. T. Rasmussen, Minneapolis

Recent Progress in the Investigation of Posterior Lobe of the Pituitary Gland.

E. P. Bugbee and O. Kamm, Detroit

A New Source of Ovarian Follicular Hormone and Some Notes on its Assay.

J. A. Morrell, J. R. Varley and H. H. Powers, New Brunswick, N. J.

Members of the Association have the privilege of inviting as guests any who may be interested in this subject. All subscribers to ENDOCRINOLOGY are invited to attend.

H. LISSER, President,
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TWELFTH ANNUAL BUSINESS MEETING

The Twelfth Annual Business Meeting of the Association for the Study of Internal Secretions will convene at 5 o'clock the afternoon of Tuesday, June 12, 1928, in the Loring Theater, Minneapolis, Minn.

The purpose of this meeting shall be to receive reports for the fiscal year ended December 31, 1927, to elect officers for the ensuing year, and to transact any other business which may come before the Association.

H. LISSER, President,
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The name of the building in which our Los Angeles office is located has been changed to the Rowan Building. Please note this change, effective June 1, 1928. A new building across the street will take the name "Title Insurance Bldg.," and this should not be used in future. The address now is 1045-6-7 Rowan Bldg., Los Angeles, Calif. This building is located at 458 South Spring St., corner Fifth Street.

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AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

As we are closing our forms for this number of ENDOCRINOLOGY, we have received a copy of the program of the annual meeting of the American Association for the Study of Goiter, to be held in Denver, Colorado, June 18, 19 and 20.

The headquarters of the Association will be at the Cosmopolitan Hotel, and the Scientific Sessions will be held at Medical Hall, 1620 Court Place.

Copy of the complete program can be had by addressing Dr. S. D. Van Meter, 1621 Court Place, Denver, Colorado, or Dr. K. W. Kinard, Bryant Bldg., Kansas City, Mo.

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Endocrinology

The Bulletin *of the*
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Internal Secretions

March-April, 1928

THE MORPHOLOGY OF PARS INTERMEDIA OF THE HUMAN HYPOPHYSIS*

A. T. RASMUSSEN

From the Department of Anatomy, Medical School, University of Minnesota

MINNEAPOLIS

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INTRODUCTION

It is very evident from such reviews of the pituitary problem as the one by Geiling (1), that we are in the midst of an

* Aided by a grant from the research fund of the Graduate School, University of Minnesota.

unusually rapid transition period with reference to the conceptions of the functions of the different parts of the hypophysis. The tendency seems to be to greatly limit the sphere of its influence.

Due to its small size and location in the interior of the organ, pars intermedia is one of the least understood parts of the gland. Judging from some of the discussions found in the medical literature, some writers lack a concrete idea of the actual magnitude of the tissue known as the intermediate portion of the human hypophysis.

The primary purpose of this note is to call attention to the great variation in the actual weight of this part of the hypophysis as determined by fairly accurate volumetric methods. The procedure consists of making serial sections of the organ and by means of a projection apparatus tracing the enlarged outline of the various portions on heavy standardized paper. These areas are cut out and weighed. If the weight of the fresh gland is known, it is easy to calculate what proportion of that weight is represented by any particular subdivision of the gland. Further details may be obtained from a previous publication (2).

IS THERE A TRUE PARS INTERMEDIA IN THE ADULT HUMAN HYPOPHYSIS?

Many investigators have commented in general terms on the small size and great variability of the intermediate lobe of the human hypophysis. Plaut (3), on this account, holds that it is a rudimentary organ in man, and hence of little or no functional significance in the human body. Therefore such conceptions as hypofunction, hyperfunction and dysfunction of this lobe have little or no foundation.

Kasche (4), while admitting that there are always chromaphilic cells in the intermediate region and closely associated topographically with the nervous lobe, does not consider that there is sufficient morphological evidence to justify its being designated a special gland concerned with metabolism. As a result of the application of the technique of Maurer and Lewis (5) on fresh human material, he was unable to find cells with the special characteristics of pars intermedia of lower animals. Like sev-

eral other investigators, he concludes that these chromaphilic cells are essentially like the basophilic cells of the anterior lobe proper.

The view that there is no pars intermedia in adult man homologous to that of lower animals is also held by Erdheim (6) and Dayton (7). On account of the unusually extensive investigations into the normal and pathological structure of the human hypophysis made by Erdheim, his views should have considerable weight. Dayton examined over 100 normal adult hypophyses and some from infants, as a result of which he concludes that either the anlage of pars intermedia of the human embryo disappears entirely or gives origin to mucous glands or to small basophilic cells, neither of which should be regarded as pars intermedia. The mucous glands disappear before the adult stage is reached. Dayton further argues that all the colloid vesicles and associated cells are derived from the anterior lobe because the cells forming the walls of these cysts may be cytologically exactly like the cells of the anterior lobe proper. He claims that in pregnancy, castration and certain pathological changes of the reproductive glands, the cells forming the walls about the colloid of pars intermedia undergo the same changes as take place in the cells of the anterior lobe.

In short, while it is conceded that there is some sort of epithelial tissue between the cleft (remains of Rathke's pouch) and the nervous lobe, or actually invading the latter, its homology with pars intermedia of lower animals is in doubt. However, at the present stage it would seem—as pointed out by Lewis and Lee (8)—that it is best to retain the term "pars intermedia" ("pars infundibularis" of the juxtaneural portion of Tilney's terminology) for this tissue and the related colloid, even if it does differ somewhat from that of animals. There are also both gross and microscopic differences in structure of pars intermedia of different animals. If it should finally be demonstrated (which is doubtful) that in man it is developed entirely from the anterior lobe, and that the posterior wall of Rathke's really disappear, then a revision of the terminology might be desirable from a morphological point of view. From a functional standpoint, nothing can be said till more knowledge of the physiological processes carried on by this portion of the hypophysis has been established in a wide range of animals.

HISTOLOGY OF PARS INTERMEDIA IN MAN

The histology of this region of the hypophysis has been worked on from various angles by many other investigators besides those mentioned here; but since several of the more recent publications give the essential literature, a comprehensive review will not be necessary. Erdheim's paper (6) contains a very extensive bibliography of several hundred titles. The clearest conception of the detailed relations and general histology is found in the recent paper by Lewis and Lee (8), which contains excellent illustrations of microscopical preparations and reconstructions, as well as a concise discussion of the related literature. Their study is based on serial sections of 30 human hypophyses, ranging in age from birth to 73 years, and on many other individual sections. Since our own work corroborates theirs, only a

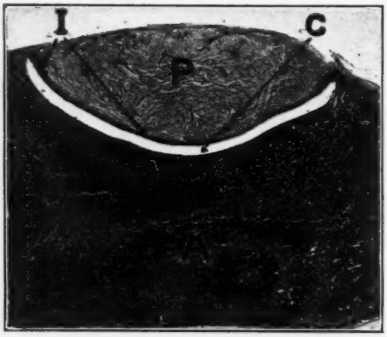

Figure 1. Photograph of a horizontal section through the middle of the hypophysis of a human newborn to show the general appearance of pars intermedia (I). A, anterior lobe; P, posterior or nervous lobe; C, cleft or residual lumen of Rathke's pouch.

very hasty sketch as deducted from the literature and from investigations that have been done in this laboratory will be given, and that merely for the purpose of giving a general background to the volumetric data to be submitted.

In the fetus, after the hypophysis has assumed its general form, there is a fairly uniform and distinct stratum of epithelial elements, several cells in thickness, between the cleft and the nervous lobe. This presents the general appearance of the pars intermedia of the usual laboratory animals, although there is

great need for further application of finer cytological technique to determine the degree of similarity that actually exists.

This condition usually persists till about birth. A general view of a newborn hypophysis is shown in figure 1. This is a horizontal section showing the general relations of pars intermedia (I), which is merely the narrow black border on the anterior surface of the nervous lobe (P), forming the posterior wall of the cleft (C). It is distinctly thicker at both lateral edges near the point where it comes in contact with the anterior lobe (A).

Fig. 2. Photograph of the intermediate region of a horizontal section through the middle of the hypophysis of a 6-year-old child to show the relation of the irregular epithelial masses and colloid to the more uniform stratum characteristic of the newborn and fetal hypophysis. I, pars intermedia containing several accumulations of colloid; A, anterior lobe; P, posterior lobe.

During early childhood much irregularity occurs, due to diverticula and tubular outgrowth from pars intermedia into the nervous lobe, as shown in figures 2 and 3, which are from a 6-year-old child. Figure 3 is at a sufficiently high magnification to show clearly the extension of pars intermedia and the residual lumen or cleft into the nervous lobe as branched tubules (D) with wide lumen. Figure 4 is a still higher power view to show particularly the appearance of some of these tubular outgrowths as seen in cross section (G). The reason why Dayton (7) and others have regarded these as mucous glands is evident. Notwithstanding the fact that there is a general structural resem-

blance to mucous alveoli and that Guizzetti (9) claims that the micro-chemical reactions of the substance which they secrete is that of the mucins, additional micro-chemical data are necessary to establish the mucous character of these tubules. The recon-

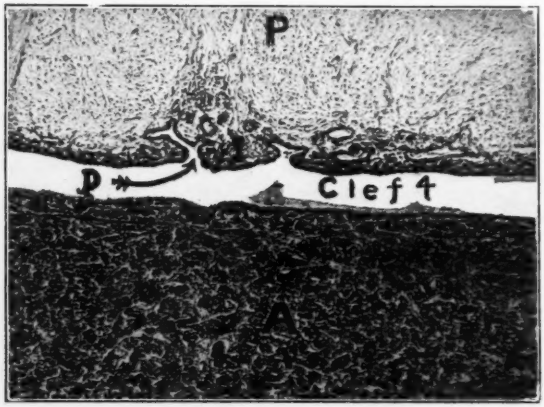

Fig. 3. Photograph of a more limited region of pars intermedia of the same hypophysis as shown in figure 2, but at a higher magnification, to show how the cells lining the posterior wall of the cleft grow into the posterior lobe (P), as tubular diverticula (D). I, pars intermedia; A, anterior lobe.

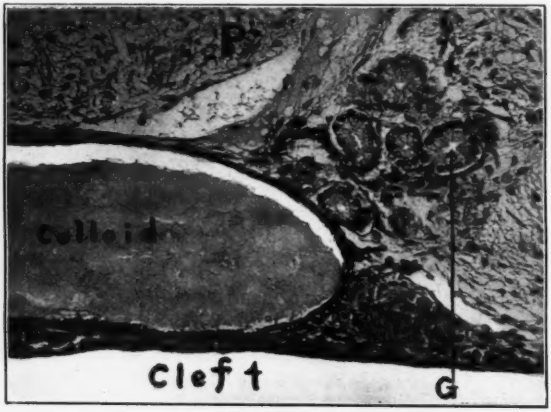

Fig. 4. Highly magnified view of a colloid vesicle or cyst and cross section of the tubular outgrowths from pars intermedia—already shown in longitudinal section and under lower power in figure 3. P, posterior lobe; G, gland-like tubules from pars intermedia in cross-section.

structions of these tubules and the detailed drawings by Lewis and Lee (8) suggest at least a glandular character.

The accumulation of a variable amount of colloid both in the cleft and in the above mentioned diverticula (see figures 2 and 4) further complicates the picture. Colloid cysts in this region may thus be derived from the accumulation of colloid in isolated portions of the cleft or in the more differentiated tubular or gland-like outgrowths. The presence of small amounts of colloid in the inner end of some of the cells lining these tubules is described by Lewis and Lee (8). This is of considerable importance in connection with the origin and significance of the colloid—a subject that is still in a very unsettled state (10). As the colloid masses get larger and larger there is a tendency for the surrounding cells to become flatter and flatter, as is seen in figure 4.

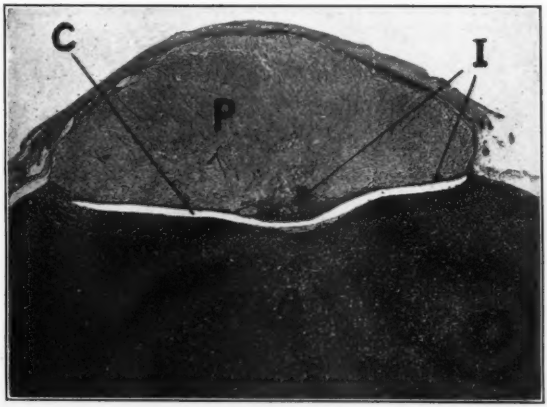

Fig. 5. Photograph of a horizontal section of the hypophysis of a 6-year-old child to show the general extent of pars intermedia (I) at the same magnification as in figure 1. A, anterior lobe; P, posterior lobe; C, cleft.

Another method of colloid formation often described, especially in the anterior lobe, but which probably also occurs in the intermediate, is by degeneration of the central cells within a group of cells. It is thus frequently impossible in the adult stage to say how much of the colloid in the region of pars intermedia should be considered a part of pars intermedia and how

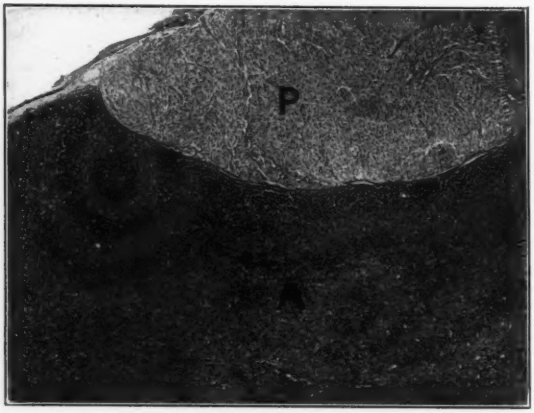

Fig. 6. Photograph of a horizontal section of a normal male adult, human hypophysis to show the extremely small size to which pars intermedia may be reduced. In this case it consists of an incomplete layer, a single cell in thickness, and hence not evident in the photography. Same magnification as figures 1 and 5. A, anterior lobe; P, posterior lobe.

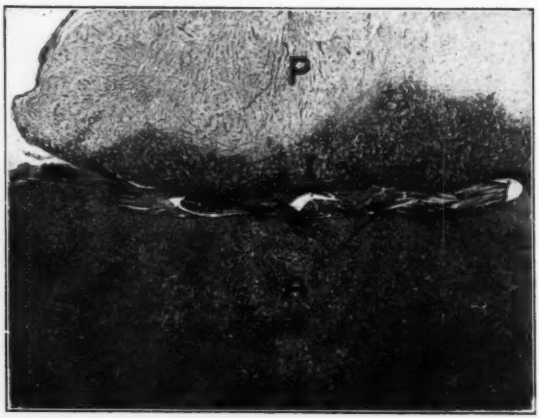

Fig. 7. Photograph of a horizontal section of a normal male adult human hypophysis to show the maximum development of pars intermedia. Same magnification as figures 1, 5, and 6. A, anterior lobe; P, posterior lobe; I, pars intermedia. The cleft is distended with colloid, which was cracked during sectioning, resulting in some pieces being displaced.

much is in the cleft proper and strictly not a part of pars intermedia.

The pars intermedia of a 6-year-old child at the same magnification as in figure 1 is shown in figure 5. The dark area extending from the central portion of pars intermedia into the nervous lobe is tissue derived from pars intermedia as just described. There is still visible a thin continuous sheet of cells separating the posterior lobe from the cleft (C). For a further description the book by Cooper (11) may be referred to.

Finally, in the adult great variability is encountered. The two extreme conditions as far as size is concerned are illustrated in figures 6 and 7, which are photographs of normal adult hypophyses at the same magnification as in figures 1 and 5, so that figures 1, 5, 6 and 7 are directly comparable. In figure 6 pars intermedia is reduced to a single layer of cells, usually less than 10 microns in thickness. The lumen of the cleft is obliterated except in a few small areas. Colloid in this particular case is also found in such small masses that they are not visible at the magnification here employed. At the other extreme, as shown in figure 7, there is an abundance of epithelial cells which form a prominent layer, usually very irregular in thickness. The amount of colloid varies greatly and is independent of the amount of epithelium. In the particular case shown here the colloid is mostly in the cleft, which may thus persist in its entirety in the adult. The tubular, gland-like diverticula are no longer visible.

The cells in the adult are still roughly divisible into three types. There are the cuboidal or low columnar cells forming a more or less imperfect stratum between the anterior lobe or the cleft, as the case may be, and the nervous lobe. Then there are the cuboidal or flattened cells which form a wall about the colloid masses that are outside of the cleft proper. And, finally, there are the polygonal and round basophilic cells scattered about in the neuroglia tissue of the nervous lobe. In figure 7 the wide, dark area (I) posterior to the cleft is composed largely of this latter type. Masses of these cells may become isolated and apparently detached from the tissue bordering on the cleft. The wide variation in the compactness of this epithelial tissue is one of the sources of error in the quantitative method here employed. A variable amount of neuroglia tissue of necessity is included in

those cases where the epithelial elements are mixed with posterior lobe tissue.

There is some difference of opinion as to the origin of these basophilic cells (7), (8), (9). They have some characteristics in common with the basophilic cells of the anterior lobe. They have been taken for neoplasms, but they are so regularly present that such a view is untenable (12).

Some of the cells lining the cleft, mostly on the posterior side, have been described as possessing cilia. They are said to occur in small patches. Bryant (13) seems to regard them as sensory elements and found them present in nearly all fresh human hypophyses examined. Strange to say such ciliated cells have never been seen in any of the series examined in this laboratory, now numbering well over 200.

THE RELATIVE SIZE OF PARS INTERMEDIA IN ANIMALS

In order to appreciate more fully the relative amount of tissue that pars intermedia constitutes in the human hypophysis, the available literature on quantitative determinations on animals might be summarized to advantage. This will be done in the order of percentage which pars intermedia constitutes of the epithelial part (pars buccalis or glandular portion) of the hypophysis. Only adults will be considered unless there is no significant difference between the percentages in young animals and adults.

Frog.—Atwell and Woodworth (14) found that in 4 specimens pars intermedia varied from 12.1% to 36.4% and averaged 24.8% of the glandular portion of the hypophysis. It is upon this form that much experimental work on this lobe has been done.

Cat.—In 5 specimens examined also by Atwell and Woodworth (14) pars intermedia varied from 11.7% to 23.3%, with an average of 16.9%.

Rabbit.—From a very comprehensive analysis of all but the pars tuberalis of the hypophysis of 61 male and 62 female rabbits, Björkman (15) found that pars intermedia averaged 15.7%.

Guinea pig.—Pars intermedia of 8 normal animals varied from 7.6% to 16.3% and averaged 10.6%, according to Rowles (16).

Albino rat.—Jackson (17) found in 4 adult males a variation from 6.6% to 13.0%, the average being 10.5%. In 4 adult females the extremes were 6.1% and 8.3%, and the average 7.2%. Slightly lower figures are given by Addison and Adams (18) on a more uniform series consisting of 7 males and 7 females weighing very close

to 200 grams each. In the males the extremes were 7.0% and 12.5%, average 9.8%, and in the females 4.8% to 7.7%, average 6.0%. Since the anterior lobe is absolutely much greater in the female than in the male, the actual weight of pars intermedia is 25 per cent more in the female than in the male in spite of the lower percentage. In neither case was pars tuberalis taken into consideration.

Urodel.—In 18 specimens belonging to 13 different species, Atwell and Woodworth (14) found a minimum of 3.6% and a maximum of 13.7%, the average being 6.8%.

Woodchuck.—In 16 males and 14 females of the species Marmota monax, the writer (19) obtained as low as 1.9% and as high as 7.7%, with an average of about 5.0%, both sexes being combined and pars tuberalis disregarded. Although pars intermedia of the male is apparently 50 per cent larger than that of the female, the data are so recorded that the variability for each sex separately cannot now be determined.

The mean values of pars intermedia has thus been found to vary in animals from 5 per cent of the epithelial portion of the hypophysis to 25 per cent. Even within the mammalian realm the range is from 5 to 17 per cent.

RELATIVE SIZE OF PARS INTERMEDIA OF THE HUMAN FETUS AND NEWBORN

Atwell and Woodworth (14) analyzed 4 fetuses ranging in age from about 7 fetal months to full term and found from 1.0 to 3.4 per cent (average 2.5 per cent) of the glandular portion was pars intermedia. A more extensive study by Covell (20) on the growth of the prenatal hypophysis of 98 specimens shows that in fetuses 25-100 mm. in length, pars intermedia represents 3.5 per cent of the glandular portion. From then on there is a slight decrease in the percentage (but, of course, an absolute increase in weight) till at birth it is only 2.4 per cent, the range being from 1.5 to 3.3 per cent, which agree well with the figures given by Atwell and Woodworth. In terms of the whole hypophysis at birth, pars intermedia represents slightly less than 2 per cent.

ABSOLUTE AND RELATIVE WEIGHT OF PARS INTERMEDIA OF NORMAL MALE ADULT HUMAN HYPOPHYSIS

The data presented here are based on a volumetric analysis of 111 normal male hypophyses from 20 to 76 years of age. The

material was obtained through the co-operation of the Department of Pathology, University of Minnesota, during a period of six years (1921-1927). For this service we wish to express our appreciation to the various members of the Pathology staff. Only perfect glands from cases of sudden and usually accidental death, where no significant pathologic change was found at autopsy, are included. Hence, it represents as nearly normal material as is obtainable. Due to the routine method of obtaining the organ, the infundibular stalk and pars tuberalis are not included. Atwell and Woodworth (14) found that pars tuberalis of the newborn may equal pars intermedia, while Covell (Thesis, University of Minnesota, 1926) in 3 adults found it only about one-half the volume of pars intermedia. Pars tuberalis being continuous with pars intermedia, with no sharp line of demarkation between them, an arbitrary plane across the stalk at the upper level of the anterior lobe was taken as the division point. This was the only consistent method of handling the material.

The 30 normal cases involved in a preliminary report (21) are included in order to increase the reliability of the results. The method and nature of individual figures are illustrated in two previous papers (2), (21). The data have been worked up by recognized statistical methods in order to test the significance of such differences in weight as seem to exist at various ages and body lengths. The writer is indebted to Dr. C. M. Jackson and Dr. R. E. Scammon for advice on statistical methods. Only approximate body weights are available, so that no attempt has been made to determine any correlation with body weight. The general observation has been that no correlation exists in human adults between weight of the hypophysis and body weight.

All the epithelial elements posterior to the region of the cleft is included under the head of parenchyma of pars intermedia. The colloid includes that which is in the cleft as well as that which is outside of the cleft proper, but in the region of pars intermedia. There seems to be no good reason for separating the colloid that is obviously within the cleft from that which is apparently outside of the cleft but in its neighborhood. The latter is so often in a recess or diverticulum derived from the cleft, and still in communication with portions of the cleft proper, that it seems best to make no distinction, although some of the colloid in the cleft may have been derived from the anterior lobe,

a subject that is discussed more fully in a previous publication (10).

Frequency distribution of the weight of pars intermedia. In figure 8 is shown the distribution of the weight of the epithelium (parenchyma). In nearly a third of the cases the weight lies between 1 and 2 mgm. In 80 of them (72 per cent of total number) it is less than 5 mgm. Only 17 of the entire 111, or 15 per cent, have more than 8 mgm., and only one has as much as 20 mgm.

Figure 9 is a similar graph showing the distribution of the colloid, the weight of which is somewhat greater, but of about

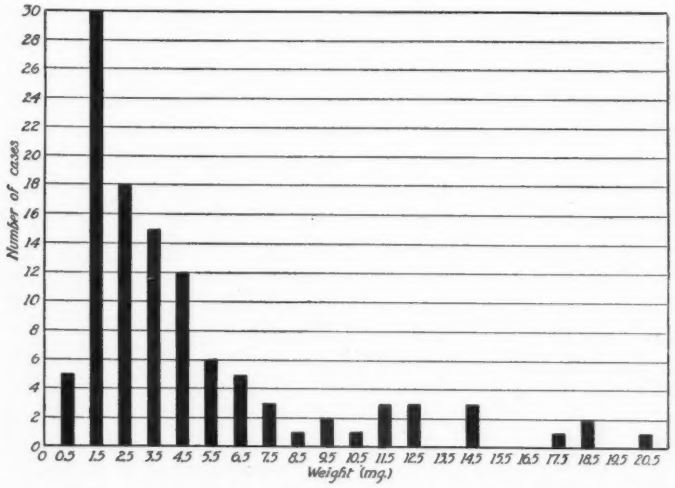

Fig. 8. Frequency graph showing the distribution of the weight of the epithelium (parenchyma) of pars intermedia of 111 normal male adult human hypophyses.

the same order, and has the same skewness towards the low values.

A frequency graph of the combined weight of the parenchyma and colloid is shown in figure 10. Even if the colloid is included as part of pars intermedia, 79 (71 per cent of total number) have less than 12 mgm. and only 9 (8 per cent) have more than 24 mgm.

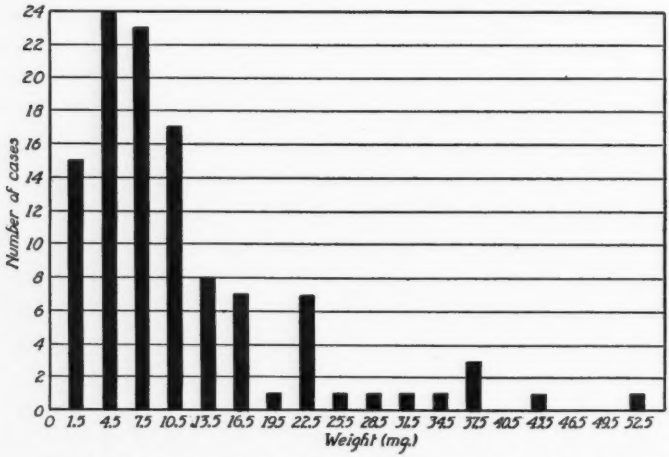

Fig. 9. Frequency graph showing the distribution of the weight of the colloid associated with pars intermedia of 111 normal male adult human hypophyses.

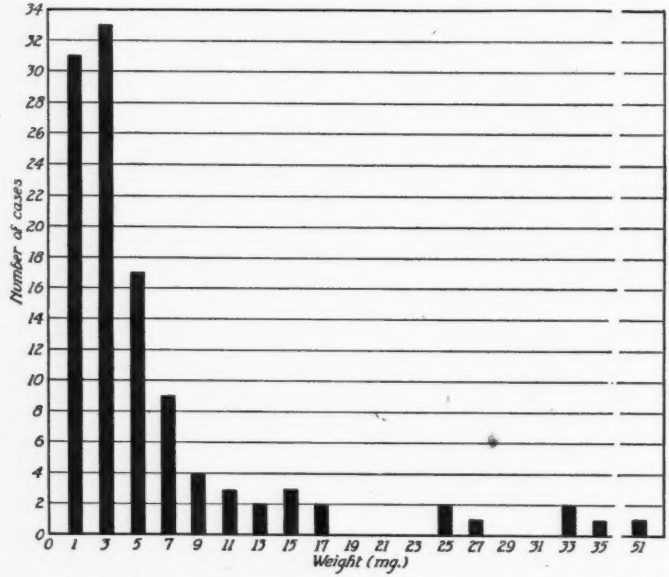

Fig. 10. Frequency graph showing the distribution of the combined weight of the epithelium and colloid of pars intermedia of 111 normal male adult human hypophyses.

Coefficient of variation. For purposes of comparison with other parts of the body, the coefficient of variation

$$\left(\frac{\text{Standard deviation}}{\text{mean}} \times 100\right)$$

has been calculated for the various parts of the hypophysis. This shows that the colloid has the extremely high coefficient of variation of 137. The epithelium of pars intermedia is next with a coefficient of 94. The coefficient of the combined weight of epithelium and colloid of pars intermedia is 89. These figures are much higher than those for the other lobes and the entire hypophysis, the coefficient of variation of which are: posterior lobe, 29; anterior lobe, 21; and the entire hypophysis, 18. The coefficient of variation of some of the other normal organs of the body are: thyroid, 45; spleen, 38; thymus, 33; heart, 18; kidney, 17; liver, 15; brain, 8 (22), (23). Thus, while the whole hypophysis has a variability about like that of heart, kidney and liver, pars intermedia is much more variable than even such variable organs as the thyroid, spleen and thymus.

Relative weight of pars intermedia with reference to the entire hypophysis and the epithelial portion only. The mean and extreme percentages of the entire hypophysis (without capsule) which pars intermedia represents are listed in the first three columns of table 1.

TABLE 1

Relative weight of the different parts and of total pars intermedia as percentage of the entire hypophysis (without capsule) and as percentage of the glandular (epithelial) portion only; 111 normal male human adults.

Components of Pars Intermedia	Per Cent of Entire Hypophysis			Per Cent of Glandular Portion		
	Minimum	Maximum	Mean	Minimum	Maximum	Mean
Parenchyma	.13	3.6	.9	.17	4.8	1.1
Colloid	.02	10.4	1.2	.02	11.3	1.6
Total	.26	10.6	2.1	.31	11.5	2.7

In order to make direct comparisons with the relative weights given for animals and human newborns, the data have also been computed as percentage of the glandular or epithelial portion of the hypophysis as shown in the last three columns of table 1. The mean value of the parenchyma in round numbers is 1 per cent (ranging from about .2 to nearly 5 per cent). This is about

2/5 of the percentage found in the newborn. But since the epithelial portion of the gland (and in fact the entire hypophysis) has increased about 5 times from birth to maturity, it follows that the absolute amount of epithelial tissue in pars intermedia has on the average actually doubled in weight during childhood.

If the colloid is reckoned as part of pars intermedia, then it constitutes essentially the same percentage in the adult as in the newborn with reference to both the hypophysis as a whole (2.1 per cent) and its glandular portion only (2.7 per cent).

In comparison with animals, the mean value for the parenchyma of the human pars intermedia constitutes about one-fifth as large a proportion of the epithelial portion of the hypophysis as the smallest mean value found in animals so far investigated quantitatively. If colloid is added, pars intermedia is about one-half as large a proportion of the gland as the minimal values in animals. As far as mean values are concerned, there should then be no serious objection to regarding this part of the hypophysis as being just as important to man as it is to some animals; but the minimum proportion (less than .2 per cent of the glandular part or, as shown in table 4, about .5 mgm. in actual weight) represents such a small mass of tissue that it is not strange to find that some investigators have regarded it as rudimentary. The percentage which this minimal weight constitutes of a 70 kilogram body is in round numbers .000001 per cent. If it were in the form of a cube, it would measure .8 mm. each way. These small magnitudes ought to be kept in mind in any serious discussion of the rôle played by this part of the hypophysis.

TABLE 2

Mean absolute weights (with the probable error) of pars intermedia, according to stature; 109 normal male human adults.

Stature cm.	No. of Cases	Parenchyma mgm.	Colloid mgm.	Parenchyma and Colloid Combined mgm.
152–170	43	4.1± .33	7.5±1.04	11.6±1.04
171–175	33	4.6± .54	6.9±1.02	11.7±1.18
176–192	33	5.1± .80	4.6± .70	9.8±1.02

Relation of pars intermedia to stature. The weight of the whole hypophysis is on the average noticeably greater in taller

individuals (21). The data on pars intermedia in this regard are shown in table 2. The 109 individuals with a record of body length have been divided into three groups according to stature. One group of 33 cases consists of those near the average in stature, leaving 43 that are distinctly below the average and 33 that are distinctly above. The parenchyma seems to increase slightly with an increase in stature, while colloid seems to decrease. However, the difference between any two groups is small and statistically not significant, as is shown in table 3. In the last column of the table the difference between groups compared has been divided by the probable error of the difference. To be

TABLE 3

Differences in the weight of pars intermedia of different stature groups and the significance of these differences.

Structure	Difference Between Means	Probable Error of Difference	Ratio of Difference to Probable Error
152–170 compared with 171–175			
Parenchyma	.7	.63	1.1
Colloid	.6	1.46	.4
171–175 compared with 176–192			
Parenchyma	.3	.81	.4
Colloid	2.3	1.24	1.8
152–170 compared with 176–192			
Parenchyma	1.0	.68	1.5
Colloid	2.9	1.25	2.3

statistically significant the resulting figure should be at least three; *i. e.*, in order to be fairly sure that the difference between two means is not due to mere chance in random sampling brought about by the limited number of cases involved and the degree of individual variation, the difference should be at least three times as great as the probable error of the difference. The formula for the probable error of the difference is

$$\sqrt{(\mathrm{PEa})^2 + (\mathrm{PEb})^2}$$

where PEa is the probable error of one of the means and PEb is the probable error of the other. A similar analysis shows that it is chiefly the anterior lobe that is responsible for the larger

hypophysis in taller men. The data supporting this statement will be available in the near future.

Relation of pars intermedia to age. The literature contains many statements on the change which pars intermedia undergoes

TABLE 4

Weight of parenchyma (epthelium) of pars intermedia, with the probable error of the mean, according to age; 111 normal male human adults.

Age, Years	No. of Cases	Minimum mgm.	Maximum mgm.	Median mgm.	Mean and Probable Error mgm.
20–30	17	.9	14.5	2.0	2.9± .55
30–40	19	1.1	14.8	3.2	4.1± .60
40–50	28	.8	20.1	3.2	4.5± .60
50–60	25	.5	18.9	3.7	4.8± .56
60–76	22	.8	17.3	4.1	5.6± .72
20–76	111	.5	20.1	3.1	4.6± .28

with advancing years. Thus Lucien (24), who studied 20 glands from 65 to 83 years old, considers it normally different histologically in the aged. The most common statement is that there is an increase in the invasion of epithelial cells into the nervous lobe in older individuals. An increase in the amount of colloid with age is also repeatedly mentioned. No test of the accuracy

TABLE 5

Differences in the weight of the parenchyma (epithelium) of pars intermedia of the different age groups and the significance of these differences.

Groups Compared	Difference Between Means	Probable Error of Difference	Ratio of Difference to Probable Error
20–30 and 30–40	1.2	.81	1.5
30–40 and 40–50	.4	.85	.5
40–50 and 50–60	.3	.82	.4
50–60 and 60–76	.8	.91	.9
20–30 and 60–76	2.7	.91	3.0

of these observations seems to have been made. General inspection may lead to erroneous conclusions where there is much individual variation.

The results of the quantitative method here employed are shown in table 4, which includes the mean values and their probable error together with the minimum, maximum and median weights according to 10-year intervals and for the entire series of 111 cases. Due to the positive skewness (towards the

low values) of the curve of distribution (figure 8), the median is in all cases distinctly smaller than the mean. Both the median and the mean increase regularly, though only slightly, with age, and thus seem to support general observations. If the significance of the differences is tested statistically, as already ex-

TABLE 6

Weight of the colloid associated with pars intermedia, according to age; 111 normal male human adults.

Age, Years	No. of Cases	Minimum mgm.	Maximum mgm.	Median mgm.	Mean and Probable Error mgm.
20–30	17	.1	51.1	2.9	8.5±2.36
30–40	19	.2	24.2	3.2	5.0± .94
40–50	28	.1	35.8	3.8	6.6±1.00
50–60	25	.2	33.1	3.6	5.6± .93
60–76	22	.6	33.1	3.4	6.3±1.21
20–76	111	.1	51.1	3.3	6.3± .55

plained, it is found (table 5) that the difference is too small, considering the relatively large probable error, to be actual proof that an increase occurs within a period of 10 years. When the youngest group is compared with the oldest group, the ratio of the difference to the probable error of the difference is 3, which is fairly good proof that there is an increase over a long period of years.

TABLE 7

Combined weight of the parenchyma and colloid of pars intermedia, according to age; 111 normal male human adults.

Age, Years	No. of Cases	Minimum mgm.	Maximum mgm.	Median mgm.	Mean and Probable Error mgm.
20–30	17	1.3	52.0	5.5	11.4±2.33
30–40	19	1.6	29.1	7.7	9.1±1.03
40–50	28	1.3	37.9	7.8	11.4±1.13
50–60	25	1.3	43.0	8.6	10.0±1.21
60–76	22	2.0	38.6	8.2	12.0±1.51
20–76	111	1.3	52.0	7.7	10.8± .62

In table 6 are recorded the data on the weight of the colloid by 10-year intervals. There is no proof here of any increase with age.

Finally, the combined weight of colloid and epithelium is shown in table 7, which indicates no significant correlation with age.

SUMMARY

While there are those who discuss the significance of pars intermedia of man as if it were of considerable importance, a number of investigators, especially in recent years, doubt the existence of a true functional pars intermedia in adult man, and consider the epithelial tissue in that region of the mature human hypophysis as a rudimentary structure or as an extension of the anterior lobe. In view of the uncertainty regarding the specific function of this structure, especially in man, it appears best to retain the name "pars intermedia" for this part of the human gland, and to tentatively assume that it is homologous with pars intermedia of animals.

The general features of the changes in pars intermedia from the late fetal stage to the adult are described and illustrated with photographs.

Quantitative data on the relative size of pars intermedia to the epithelial portion of the hypophysis of various animals are reviewed. The mean values run as high as 25 per cent (in frogs) to as low as 5 per cent (in the woodchuck).

In the human newborn pars intermedia represents about 2.5 per cent of the epithelial portion of the hypophysis.

Data on the absolute and relative weight of pars intermedia of 111 normal male human adults (nearly all from cases of sudden accidental death) are presented with the view of giving a concrete idea of the variability and the exceedingly small amount of tissue that it may represent in some healthy individuals.

The epithelial portion (parenchyma) of pars intermedia was found to average .9 per cent of the whole hypophysis, varying from .13 per cent to 3.6 per cent. As percentage of the glandular portion of the hypophysis the corresponding figures are: average, 1.1 per cent; minimum, .17 per cent; maximum, 4.8 per cent. This is about 2/5 of the proportion found in the newborn.

The colloid associated with the intermediate region of the hypophysis averaged 1.2 per cent of the entire hypophysis, the minimum being .02 per cent and the maximum being 10.4 per cent. As percentage of the epithelial portion of the hypophysis, the corresponding figures are: average, 1.6 per cent; minimum, .02 per cent; maximum, 11.3 per cent.

The weight of the epithelium of pars intermedia averaged 4.6 mgm. (about twice the amount found in the newborn), varying from .5 mgm. to 20.1 mgm., the coefficient of variation being 94.

The weight of the colloid averaged 6.3 mgm, varying from .1 mgm. to 51.1 mgm., the coefficient of variation being 137.

The combined weight of the epithelium and colloid averaged 10.8 mgm., varying from 1.3 mgm. to 52.0 mgm., the coefficient of variation being 89. This means that pars intermedia, whether the colloid is included or not, is probably the most variable organ in the body, if it is a special organ.

The distribution curves for both portions of pars intermedia are so skewed toward the lower weights that the median values are from 29 to 48 per cent smaller than the mean (average) values given above. The median for the epithelium is 3.1 mgm.; for the colloid, 3.3 mgm., and for the two combined, 7.7 mgm. These probably represent a truer measure of the central tendency than the mean or arithmetic average.

The minimal weight (.5 mgm) of the epithelium of pars intermedia represents a mass no larger than a cube .8 mm. in dimensions, while the average (4.6 mgm.) would make a cube slightly less than 1.7 mm. in size.

The epithelium of pars intermedia of the adult seems to gradually increase with age. Statistically the proof is significant only when those under 30 years of age are compared with those over 60 years.

There is no evidence that the colloid in the region of pars intermedia increases with age in adults.

There is no significant correlation between stature and weight of pars intermedia.

There is no correlation between the amount of epithelium and amount of colloid in pars intermedia.

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ESTROGEN, A NEW SEX HORMONE: ITS CLINICAL USE, WITH CASE REPORTS*

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For a long period after the introduction of ovarian substances into medicine, the therapeutic results were uncertain. Glandular products heretofore, not questioning their pureness or exact site of origin or method of extraction, had to depend solely upon empirical testing for estimate of their potency. This is in contrast to drugs like digitalis and belladonna, for which we have a definite biological means of assay and are certain of the exact potency for a given dose. Faulty methods of manufacturing were primarily responsible, as there were no analytical methods for assaying these glandular products before placing them on the market for use in medicine. Estrogen, an extract of human placenta containing ovarian hormone will be presented as an illustration of a glandular product that has been assayed by definite biological methods.

The demonstration by Stockard and Papanicolaou of "the existence of a typical estrus cycle in the guinea pig, with a study of the histological and physiological changes," gave the basis for an assay of ovarian activity which has in ten years contributed more to our knowledge of ovarian hormone than all preceding research. These authors devised a biological test in which castrated mice are used to determine the presence of the sex hormone in the circulating blood. The test consists of a study of the vaginal spreads stained with a one per cent aqueous solution of thioin at twenty-four, forty-eight and sixty hours after the injections of the sex hormone and noting the character of the cells. A positive smear, which signifies the presence of the sex hormone in the circulating blood, that is one mouse unit, consists of a great preponderance of non-nucleated squamous scales, possibly some nucleated vaginal epithelial cells, but no leukocytes. This is the picture corresponding to that of normal oestrus in mice.

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By means of this biological test the Allen-Doisy follicular hormone has been studied, its estrus stimulating effects ascertained, the site of its production discovered and ovarian products containing it standardized. Using this method of assay, Frank and Goldberger, Gustavson and Weyerts have demonstrated the presence of, and extracted the hormone from, the blood of the sow and human female.

Furthermore, it has been demonstrated that the functional mechanism of the menstrual process may be markedly influenced by the administration of substances derived from the two sources in the ovary, the follicular fluid and the corpus luteum, each of which has its specific hormone, which is elaborated at the time of puberty.

The cyclic phenomenon, estrus, occurring in the female, particularly in the lower orders, has been shown with reasonable certainty to be due to a hormone found principally in the follicular fluid of the matured Graafian follicle. Allen and Doisy extracted this hormone from follicular fluid and induced estrus in castrated female rats. This principle is used in assaying the activity of such preparations. They found it contained in preparations of placenta and in ovaries, from which the liquor folliculi had been removed, as well as in the liquor folliculli itself and corpus luteum.

Frank and Goldberger have shown that the follicular hormone progressively increases in concentration in the blood of the normal non-pregnant human female for a period of from ten to fifteen days before the onset of menstruation, disappearing at that time from the general circulation and appearing in the menstrual blood. The attainment of the maximum concentration of the hormone corresponds with the onset of menstruation and suggests that it induces it. In pregnant women the maximum concentration corresponds with the beginning of labor.

Besides this estrus inducing follicular hormone, Papanicolaou has isolated a luteal hormone which represses estrus and menstruation and accounts for the inhibiting action of the persistent corpus luteum in pregnancy. In the non-pregnant female this hormone of the corpus luteum may by its abnormally excessive production and persistence so diminish the effect of the follicular hormone as to give rise to amenorrhea.

Both before and following the development of the biological test many tissue extracts were investigated. One of the striking results of research of this kind was the demonstration by Herrmann of the follicular estrus producing hormone in the placenta. This work has been verified by such workers as Aschner, Allen and Doisy and Frank and Gustavson. Two theories are proposed to account for the presence of this estrus inciting hormone in the placenta: one that it is secreted by the placenta and the other that the placenta extracts the hormone from the blood. The latter theory seems the more probable, for Parkes and Bellerby point out that estrus never occurs during normal pregnancy and that estrus artificially produced in pregnant animals by the injection of follicular hormone causes abortion and reabsorption.

The fact that corpus luteum is evidently able to secrete both hormones, the estrus inciting sex hormone and the luteal inhibiting hormone has not received general recognition. However, Frank, Bonham and Gustavson have shown that the female sex hormone, whether obtained from follicle fluid, corpus luteum or placenta, can be freed of all nitrogen, phosphorus, cholesterol and cholesterol reactions; and that from whatever source derived, it shows the same chemical properties and composition and gives a similiar reaction on the contraction rate of the isolated uterus of the rat. Doisy corroborates this statement.

Using the biological test and method of assay prescribed by Allen and Doisy, the research department of one of our larger pharmaceutical houses at first isolated a product called Estron, which was an extract of the fluid obtained from the follicles of hog ovaries, no other product of the ovary being used. They apparently had a great deal of difficulty in collecting and standardizing this product for its physiological potency, and have developed in its place Estrogen, which has the same physiological properties but has the advantage over Estron in that it can be prepared on a practical basis with a greater potency as measured by the rat unit method of standardization.

Estrogen is a colloidal solution of human placental extract containing ovarian hormone. It is of the emulsoid type, with an opalescent appearance. Upon being allowed to stand, certain of the elements may separate, but they can be again emulsified by

shaking without any impairment of activity. It is intended for subcutaneous injection and not for intravenous use.

Chemically, each cubic centimeter was found to show:

Total solids	2.75 milligrams
Total nitrogen	0.065 milligrams
Amino-Nitrogens	0.018 milligrams
Biuret test	Negative
Hydrogen ion concentration	5.5 to 6.0

The above values will vary with different lots, because the basis of standardization is physiological activity and not content of solids. One cubic centimeter represents from five to ten cc. of fresh follicular fluid.

Typical estrus has been produced in ovariectomized rats by subcutaneous injections of this extract. The effect is made use of in standardization of the product. They have adopted for the unit of potency the "Rat Unit," originally proposed by Allen and Doisy. One rat unit is the minimum amount which will produce estrus in an ovariectomized rat of 140 grams. Eight injections are given, four daily, for two days, estrus being determined by examining the cell forms found in the vaginal smear taken from the rats on the third and fourth days of the test. Estrogen is a sterile aqueous solution, and has been found to be non-toxic even in enormous doses, nor does it give signs of protein reaction.

Estrogen is suggested especially for use in functional amenorrhea, the subjective disturbance of either natural or artificial menopause, sexual frigidity, delayed puberty, lack of development of the secondary sex characteristics, and in some cases of mental depression.

The proper dose and interval between injections of Estrogen have not yet been definitely determined. Based upon physiological research work, it is suggested that doses of one to two cc. of Estrogen be administered daily for six or eight days, theoretically a few days prior to the expected date of menstruation. No further treatment is suggested after the administration of a series of injections until the next menstrual epoch. Subsequent treatment will of course depend upon the response obtained. It may be necessary to continue this plan of treatment, increasing the size or interval of dose as indicated. Estrogen is fur-

nished for experimental purposes in one cc. ampoules, packages of twelve.

CASE REPORTS

I have had the opportunity of working with Estrogen since January, 1927, and have had under my observation twelve cases, demonstrating vaso-motor and nervous manifestations, the result of scanty or absent menstruation, and submit herewith six typical case reports.

CASE 1: Mrs. J. Mc., age 47. For the past five years the patient had been troubled with irregular menses associated with a burning sensation on top of the head, marked nervousness and pains in the back and legs. General physical and pelvic examinations were negative. She was treated for menopause with corpus luteum extract (5 grains) for a period of one year, with only slight improvement. At the menstruation period in January, 1927, the patient came in with marked aggravation of symptoms and was given a course of eight injections of Estrogen (1 cc.) intramuscularly every other day, with almost immediate relief of symptoms, and when last seen in December, 1927, had had no recurrence.

CASE 2: Mrs. V. H., age 42. Menses stopped at the age of forty and she had since been troubled with severe occipital headaches, nervousness, hot and cold flushes. There was no operative history. The patient had been treated with Varium (5 grains) three times daily, orally, without relief. She was given a course of eight injections of Estrogen, one every other day, with excellent results, but would get a recurrence of symptoms when the treatment was stopped.

CASE 3: Mrs. H. C. B., aged 54. The menses were stopped for the past eight years. The patient had since been troubled with severe hot and cold flushes, increase in weight, periodic occurrence of wheal-like rash, severe attacks of nausea, vomiting and fainting spells. Her condition was relieved by Hormonotone with Pituitary Extract during 1925 and 1926, and this last year the attacks have been controlled by Estrogen (1 cc.) at weekly intervals. The weight has become stabilized.

CASE 4: Mrs. N. A. R., aged 42, had been troubled with the appearance of irregular wheal-like areas about the face, neck and the upper chest, and an associated puffiness of the lids, swelling of the tongue and tightness in the chest. History was given of irregular, scanty menstruation, hot and cold flushes, nervousness and increase in weight. The condition was diagnosed as menopause with angio-neurotic edema. The nervous manifestations were relieved during the years 1925-1926 by giving Corpus Luteum Extract (1 cc.) intravenously at weekly intervals, but the swellings would recur. In January, 1927, Estrogen (1 cc.) was given intramuscularly with relief of hot and cold flushes and swellings. Menses stopped and the patient later developed signs of broncho-spasm. This patient belongs to a hypersensitive group.

CASE 5: Mrs. W. C., age 34. There was a history of a pelvic operation seven years ago, and the patient had since had scanty menstruation, associated with severe cramping pains in the right lower abdomen and excruciating occipital headaches, causing her to be bedridden. There were also hot and cold flushes and increase in weight. Prior to the present observation the patient was studied for foci of infection. The eyes were refracted. The Wassermann and pelvic examinations were negative. There was no history of migraine in the family. The condition was diagnosed as headaches due to ovarian deficiency, and has been relieved this last year by giving Estrogen (1 cc.) intramuscularly for three days prior to and up to beginning of menstruation. The patient has since been able to work throughout her periods, headaches are practically gone, and she required no treatment for the past three months.

CASE 6: Mrs. G. R., age 26. Menstruation started at the age of fifteen, was always irregular, often skipping several months, and was very scant, with barely more than a one day flow. Associated with this the patient had asthmatic attacks and fainting spells, especially marked at the time of the periods. In January, 1927, the patient was given a treatment of Estrogen, receiving injections once weekly and one injection at the start of menstruation. The nervousness and fainting spells were lessened and in September, 1927, she had a menstrual flow that lasted two days and was more profuse than usual. The patient was well for the following two months and then left for New Zealand. A report from her indicated that her asthma is worse, but she makes no mention of the character of the periods.

SUMMARY

1. A biological test and method of assay has been introduced and established for the preparation of glandular products—particularly those relating to ovarian activity.

2. Estrogen is a biologically assayed product of human placenta containing ovarian hormone.

3. Estrogen has been found clinically in six cases to relieve the nervous functional manifestations of ovarian deficiency.

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THE EFFECT OF ADRENALIN ON SUGAR METABOLISM

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URBANA

According to most investigators (1) adrenalin increases heat production and raises the respiratory quotient, thus indicating an increase in sugar metabolism. The object of this investigation was to determine directly the effect of adrenalin on sugar metabolism. Practically all the work that has been carried out with adrenalin has been done on the mammal with its various organs and glands of internal secretion where the situation is very complex. In this investigation we have attempted to simplify matters by using single celled animals and adding the adrenalin directly to the sugar solutions containing these animal cells and studying the effect on the rate of sugar utilization. The animal cell used was Paramecium caudatum. The paramecia were raised in great numbers on an infusion of alfalfa, pond lily leaves, and lake water. They were collected and washed free of debris by the use of a small centrifugalizing machine. The centrifugalizing tubes were graduated in cubic centimeters, so the paramecia were measured as they were collected. Sugar determinations were made according to the method of Benedict. Air was kept bubbling through the liquid containing the paramecia to insure an adequate supply of oxygen.

The following is the description of a typical experiment. Forty cubic centimeters of paramecia were collected and measured as described above. These were added to 800 cc. of aerated lake water and 800 mgm. of dextrose was dissolved in the liquid. This 800 cc. batch of paramecia-sugar preparation was divided into eight portions of 100 cc. each. The 100 cc. portions were introduced into sedimentation glasses and air was bubbled through them. To one portion 1 cc. of a 1 to 1000 adrenalin chloride solution was added making a dilution of 1 to 100,000

of adrenalin. Similarly quantities of adrenalin were added to the other 100 cc. sugar-paramecia preparations sufficient to make the dilutions indicated in Fig. 1. One portion to which no adrenalin was added served for control. Sugar determinations were made immediately and subsequently at intervals. It will be seen in Fig. 1 that the control used 39 per cent of the sugar in twelve hours; that relatively strong solutions of adrenalin, 1 to 100,000 and 1 to 200,000 decreased sugar metabolism, but the weaker solutions 1 to 1,000,000, 1 to 24,000,000 and 1 to 40,000,000 increased it while still weaker solutions, 1 to

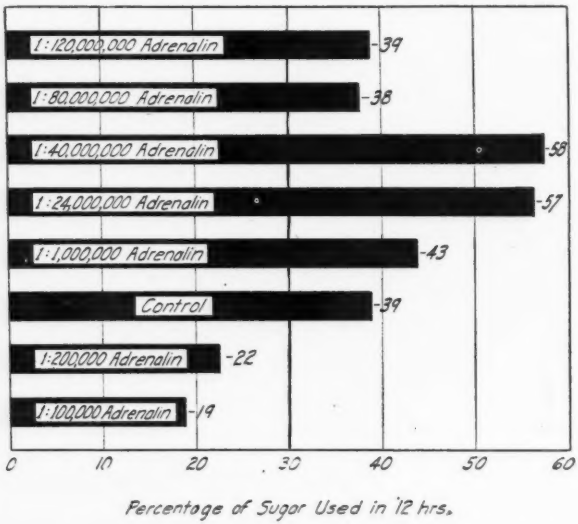

Fig. 1. Chart showing the effect of various amounts of adrenalin on the rate of sugar utilization by paramecium.

80,000,000 and 1 to 120,000,000 had no effect. The decrease in sugar metabolism brought about by the stronger solutions is attributed to the so-called toxic action of adrenalin while the weakest solutions were ineffective because of their great dilution.

During the past year and a half we have carried out a great number of experiments similar to the preceding with com-

parable results. It was observed that the adrenalin in the various portions of the 100 cc. paramecia-sugar preparations was oxidized during the experiments as was indicated by the fact that the preparations became reddish in appearance. The doses of adrenalin were accordingly repeated every hour to offset this destruction and to insure, as far as we could, the presence of adrenalin in the preparations at all times.

Hoskins (2) found that different size doses of adrenalin had different effects on blood pressure just as we find to be the case on sugar metabolism. He found that small doses of adrenalin produced a fall in blood pressure and large doses a rise, whereas, we find small doses, if large enough to be effective, increase sugar metabolism and large doses decrease it.

Two questions might be raised in this connection: First, did the paramecia use the sugar in these experiments, or was it yeast or bacteria? Second, will these results obtained with paramecium hold for the higher animals and man? The first question can be answered by stating that we have found that if the paramecia be removed by centrifugalization during an experiment, sugar utilization ceases. The second question can be answered only indirectly. We (3) have found that paramecia use all three of the simple sugars just as do the higher animals and that they use dextrose and levulose more rapidly than galactose, again resembling the higher animals and man. It was also found that insulin increased the rate of utilization of sugar by paramecium just as it does in man.

SUMMARY

Experiments were carried out, adding adrenalin to cultures of paramecia in dextrose solution. It was found that small amounts of adrenalin increase sugar metabolism, while large amounts decrease it.

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ON THE GRADED RELATION BETWEEN THE INTENSITY OF HORMONE ACTION AND THE CHARACTER OF THE RECIPIENT TISSUE

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In the following paper it is not our desire to give a detailed description of the sexual cycle of the guinea-pig. Previous publications (1) have dealt with various phases of this problem, and we intend to return to some questions relating to cyclic changes also in a future publication. In this paper we wish to draw attention to a condition observed by us in the sexual cycle of the guinea-pig, the significance of which is, however, not restricted to the sexual cycle, but which applies to the relation in general between the hormone and the substance on which it acts. Inasmuch as our conclusions are based largely on a study of the cyclic changes which occur in the cervix of the guinea-pig, it will be necessary first to give a brief description of the cervix uteri of this animal.

We may divide the cervix into three parts: (1) The vaginal cervix, or the cervical canal; this is a continuation of the vagina and represents a fairly straight canal. On the whole it behaves like the vagina, but the processes which take place in the latter are somewhat moderated here. The portio uteri which joins the vagina to the cervical canal behaves very similarly to the vagina. (2) The middle cervix, usually represented by a widening of the canal, the lumen of which is largely filled with branched papillæ. (3) The uterine cervix, the lining of which in certain respects begins to resemble the uterine mucosa; however, the epithelium of this part is of a vacuolar character similar to that found also in the middle cervix, and under certain conditions even in the vagina, although in the latter place, even if the epithelium is vacuolar, it usually has some distinctive characteristics of its own. On the other hand, scattered areas of cylindrical, vacuolar epithelium, resembling the epithelium of the uterine cervix, may also be found in the uterine mucosa at various periods.

The greater similarity between uterine cervix and uterus is still more strongly accentuated through the fact that in the uterine cervix the formation of glands, similar to those found in the uterus, begins. In the medium cervix we find, corresponding to these glands, epithelial invaginations situated between the papillæ and covered with an epithelium which is less coarsely vacuolar than the epithelium lining the papillæ. In the vaginal cervix there is, under some conditions, below the cylindrical layer a single layer of cuboidal or flat cells, while in other cases there may be several layers of the latter cells, the findings varying with the amount of growth hormone acting on the epithelium. In the middle and uterine cervix also there may be, at certain periods and in certain places, a layer of flat cells below the cylindrical layer; but in other places this may be lacking. In these parts as well the variations which occur in the character of the epithelium are in accordance with the period of the sexual cycle at which we observe the tissue, and also in accordance with the quantity of growth hormone which has been active.

The connective tissue in the different parts of the cervix also shows transitions between the connective tissue of the vagina and that of the uterus. Thus, it is fibrous in the vagina, more or less cellular in the uterine mucosa, and intermediate in character in the cervix; here it is more fibrillar than in the uterus, but not quite so fibrous as in the vagina. A greater number of cells and a diminution in the fibrous character of the connective tissue are found especially in the uterine cervix and in the papillary part of the middle cervix. On the whole, the cervical connective tissue resembles the connective tissue of the vagina more perhaps than that of the uterus; but, as stated, a certain gradation in its character in the different parts of the cervix is noticeable.

We shall now briefly describe the effects of the hormone action on the various parts of this canal at various stages of the sexual cycle. It is our purpose rather to define the principal changes, as far as they serve to illustrate our main conclusion, than to give a detailed description of the cycle.

A. *The stage preceding ovulation.* This is the period during which an active proliferation is taking place in the vagina which leads to the production of a well developed keratinized squamous

epithelium. A very marked mitotic proliferation begins in the lowest row of the epithelium, and it progresses until the highest layers have become transformed into keratin. When a thick layer of keratin has thus been produced, active mitotic division may at first still continue in the vaginal epithelium, but soon mitoses diminish in number. It is only the lowest layer of cells which proliferates in this way and forms keratin; the upper cylindrical layer remains passive, being merely raised up by the underlying squamous epithelium. Simultaneously with the proliferation of the vagina, there begins also a proliferation of the vaginal portion of the cervix, but it is less marked than in the vagina. Mitoses occur in the low cuboidal epithelium which rests on the connective tissue of the vaginal and also of the middle cervix; they may also be found in the cylindrical vacuolar epithelium which lies on top of the lower epithelium, or which may be in direct contact with the connective tissue. However, the number of cell rows is less in the vaginal cervix than in the vagina. The cuboidal epithelium at this period extends also into the uterine cervix, although there may be places here where it is lacking. Mitoses may also occur in the glands of the uterine cervix.

As far as the connective tissue is concerned, it becomes in the uterine cervix somewhat more cellular and less fibrous than it is in the vagina. However, in the uterus the connective tissue is still more cellular than in the uterine cervix.

When much keratin is produced in the vagina, oestrus changes may be noticeable in the uterus, namely, a greater height of the cells in the surface epithelium with mitoses, which extend also to the upper gland ducts. The mitoses, however, occur only in those areas of the epithelium where the cells are more solid and cuboidal, whereas the areas of higher cylindrical, more vacuolar epithelium, resembling that of the cervix, do not usually undergo mitotic proliferation. Underneath these latter areas a more edematous condition of the connective tissue may be noticeable and some collections of lymphocytes may also be found. The edematous condition of the connective tissue seems to favor the formation of papillæ in the uterine mucosa. As we observed previously, the mammary gland, as a rule, is proliferating at this period of the cycle.

B. *The stage directly following ovulation.* During this period the proliferation in the vagina decreases very markedly, and, in some cases, it may apparently be lacking. However, it seems that in certain places, especially in the region near the cervix, the number of mitoses remains still greater than elsewhere in the vagina. The keratin is cast off at this time, either at the beginning of the period or a little later, and with it the layer of cylindrical vacuolar cells lying on top of the keratin. These cylindrical cells, and especially their nuclei, now appear shrunken, owing to the insufficient supply of oxygen which they have received. Probably as the result of the diminished proliferation at this period, the mass production of keratin in the upper layers of the epithelium has ceased and we begin to notice instead a hyalinization or keratinization of individual epithelial cells, likewise situated in the upper layers of the epithelium; they also are insufficiently supplied with oxygen or other food stuffs. The gradual desquamation of these cells underneath the sheets of keratin may account for the fact that the latter is cast off in toto. As the result of the stage of proliferation in the preceding period, papillary processes of the vaginal epithelium, reaching into the connective tissue have developed, and in the center of some of these a formation of keratinizing epithelial pearls may take place. Lymphocytes and also polymorphonuclear leucocytes, unrestrained by the protective layer of keratin, migrate at various points into the lumen of the vagina; they collect here and may be observed, together with desquamated particles of keratin and with phagocytic cells, which latter take up the leucocytes.

In the cervix, conditions are transitional between those in the vagina and in the uterus. In the portio the epithelium is of about the same character as in the vagina, although the squamous epithelium may be slightly lower in the former. In the vaginal cervix, the cervical duct, proliferation has also taken place and mitoses may still be found, even in cases in which they are lacking or very rare in the vagina. Here, too, proliferation has led to the formation of keratin, on which the layer of cylindrical epithelium rests. A part of the keratin, with cylindrical epithelium, may be cast off, especially in the lower (distal) part of the cervical canal, whereas in the proximal portion which approaches the middle cervix the keratin may still be found adherent to the

squamous epithelium, and the cylindrical epithelium, on its part, is here still adherent to the keratin. In those places, where the keratin is adherent, the squamous epithelium is less thick and the keratin thus has developed somewhat later than in the more distal portion of the sex duct, which accounts for the fact that the processes are less advanced in these more proximal areas. The keratin formation may in some cases reach even into the beginning of the middle cervix, the cavity which is filled with papillomatous formations, but here the keratin formation soon ceases; in other cases it extends merely into the vaginal cervix. At this stage we may also find here and there in the upper layer of the epithelium in the vaginal cervix, epithelial cells which hyalinize or undergo certain phases of keratinization. This process takes place instead of keratinization en masse, leading to the formation of sheets of keratin, which was observed in the preceding period. In the middle cervix the layers of squamous epithelium diminish in number, and on the top of the slender papillæ, in the dilated portion of the cervix, the squamous epithelium, underneath the cylindrical epithelium, may be lacking altogether or be very low, consisting merely of one or two rows of cuboidal or flat cells. Gradually the squamous epithelium may entirely disappear and the layer of cylindrical epithelium may rest directly on the connective tissue, a condition increasingly found the nearer we approach the uterus. But even in the uterine cervix there may be, in places, one or even two layers of flat epithelium below the cylindrical epithelium, individual variations existing in this respect.

The glands begin to develop in the uterine cervix, and in certain animals they may reach even into the adjoining margin of the middle cervix. Mitoses may occur in these glands, but on the whole they seem to be less frequent than in the uterine glands. Where the glands begin, the mucosa is usually somewhat richer in connective tissue cells, although it does not as yet attain the cellular condition which we find in the uterine mucosa proper. Lymphocytes may enter the epithelium of the cervix at various points; also polymorphonuclear leucocytes frequently migrate through the cervical mucosa, especially in places where there is no keratin to exert a protective effect. These leucocytes

may injure the cylindrical epithelium and cause or increase the vacuolization we find in these cells.

The great majority of the animals which we examined had not copulated, but in those animals in which copulation had taken place conditions were essentially similar to those found in the other group. However, in the former a vaginal plug developed and, following copulation, large masses of polymorphonuclear leucocytes migrated through the vaginal wall, where the keratin layer was lacking. Also in the portio of the cervix, leucocytes may invade and migrate through the epithelium in such large masses that the epithelium is destroyed in certain areas and ulcers may develop. On the whole, the leucocytic migration is more marked in the cervix than in the vagina. Small nodules of lymphocytes too are found in the cervical mucosa, and in the uterine cervix lymph vessels may here and there be filled with lymphocytes.

In the uterus we may find at this period high cylindrical epithelium in which mitotic activity is proceeding; mitoses are also found in the gland ducts where they enter the surface epithelium and are enlarged. There may also be a few mitoses in the connective tissue of the mucosa. Many polymorphonuclear leucocytes migrate through the epithelium and may injure it. Especially following copulation, polymorphonuclear leucocytes may exert a destructive effect on the epithelium and spermatozoa may be found in the gland fundi. Lymphocytes also migrate through the mucosa into the epithelium. Patches of mucoid epithelium, with a structure corresponding to that found in the uterine cervix, may be seen after the rupture of follicles. In the majority of cases mitoses are also found in the mammary gland at this period.

C. *The sex organs during the period from the first day following ovulation to the onset of the new cycle.* (1) *The vagina.* Soon after ovulation, as we have seen, the keratin is cast off and the proliferation of the epithelium almost ceases, or at least it becomes very slight. Accordingly mitoses may be absent, or, if present, they are not very numerous. They are found especially in the broad papillary processes, which the epithelium sends downward into the connective tissue, and they may also be more frequent in the region near the cervix. As a result of this diminution in epithelial proliferation and associated with it,

there is a corresponding diminution in the number of layers of squamous epithelium and a change in the character of degeneration in the upper layers of the epithelium. Both of these processes are merely an accentuation of the alterations which began in the period directly following ovulation. The number of cell rows which can be observed varies between one and three or four. Sometimes we find only a single layer of cuboidal or flat cells, covered by a layer of cuboidal or cylindrical cells in which individual cells have undergone hyalinization or a beginning keratinization. In other cases there are two or three layers of squamous epithelium, and on top again there is a layer in which cells hyalinize or keratinize. Especially following the sixth day, the epithelium may be very low. During this latter period mitoses apparently occur in the upper rows of the epithelial cells. Also some occasional amitoses are seen here. Instead of the formation of connected sheets of keratin, such as we find in the earlier period, we again observe merely processes of hyalinization, or perhaps of partial keratinization of individual cells in the upper row of the epithelium. These cells keep their nuclei during the degenerative processes and are then cast off as isolated, nucleated cells into the lumen of the vagina; but occasionally a row of upper cells may undergo these changes simultaneously and be cast off as a layer of nucleated cells. At other times we find merely a remnant of squamous epithelium deprived altogether of hyalinizing cells. The typical keratinization occurs only if we have to deal with a relatively rapid growth of epithelium, when, as a result of this active proliferation, the upper layers of cells are quickly raised up and thus removed from the source of oxygen supply and of food stuffs. If the distance between the vessels and the upper rows of the epithelium is quite short, and the process of raising up takes place slowly, a more incomplete necrobiotic change leading to hyalinization or partial keratinization of cells, which still keep their nuclei, takes place. As stated, in some cases merely some cuboidal or low cylindrical cells develop in the upper row which do not show any sign of hyalinization.

Towards the end of the sexual period, at about the fifteenth day or somewhat later, following ovulation, a new active proliferation in the vagina, leading to typical keratin formation, may set in. We have observed this event so far only after degen-

eration of the corpus luteum of the preceding cycle has begun. Whether it may occur also at a time when the corpus luteum of the preceding cycle is still functioning remains to be seen. It is the epithelium nearest the connective tissue which proliferates when the stimulus, emanating from the growth substance, reaches it. In consequence of this proliferation the upper cell row is raised passively and becomes the layer of cylindrical epithelium which we later find covering the squamous, keratinized epithelium.

Whereas in the first period of the cycle we find a migration through the epithelium, especially of the polymorphonuclear leucocytes, somewhat later the lymphocytes become prominent; they may invade the epithelium and cause localized injury of the epithelial cells. In addition, some nodules of lymphocytes may be found in the connective tissue beneath the layer of epithelium.

(2) *The cervix.* (a) *The vaginal and middle cervix.* As compared with the conditions which obtain during oestrus, we find in the vaginal cervix a diminution in the height of the squamous epithelium and in the number of rows of flat or low cuboidal cells which corresponds to that observed in the vagina; however, in accordance with the general rule stated, the number is smaller in the vaginal cervix than in the vagina. In addition there takes place a gradual lowering in the height of the squamous epithelium in the direction from vagina to middle cervix. Near the vagina there may still be several rows of epithelium, the upper layer being formed of cuboidal or low cylindrical cells in some of which, here and there, some hyaline changes may take place; but a little higher up in the vaginal cervix the width of the squamous epithelium decreases, until only one or two rows of flat cells are found, covered by a layer of well developed vacuolar cylindrical cells. At a still greater distance from the vagina, the flat cells, which are in appearance not unlike connective tissue cells and which are situated underneath the layer of cylindrical cells, disappear altogether and the layer of cylindrical vacuolar cells rests directly on the connective tissue. This condition prevails especially in the middle cervix, although even in this portion of the cervix there may in places appear a second layer of flatter cells below the cylindrical layer. Where processes are sent by the epithelium down into the connective tissue, and where some cells are pushed below others,

the appearance of squamous epithelium may be simulated. At other points an epithelial process may push laterally into the superficial layers of the connective tissue and may thus be separated from the surface epithelium by a thin strip of connective tissue.

As in the period preceding and directly following oestrus, there is also during the remainder of the sexual cycle a formation of papillæ, which is especially marked in the middle cervix, but which, in a less pronounced way, may begin already in the vaginal cervix. The papillæ in the cervical cavity are perhaps no longer as slender as they were at the time of oestrus, but again the epithelium at the top of the papillæ is more vacuolar, propably owing to the edematous condition of the papillæ. Also in the recesses between the papillæ the epithelium is now, as it was during the oestrus period, more solid than in other places. and it thus resembles the epithelium of the glands which develop near by in the uterine cervix. Mitoses are present in the cylindrical surface epithelium of the middle and also of the vaginal cervix, and in the epithelium of the recesses mitoses may likewise occur. In addition, there are found during this period in the middle cervix, underneath the epithelium of the papillæ, very large vacuolar cells, the character of which, whether they consist of connective tissue or of epithelial cells which were pushed downward into the subjacent layer of the connective tissue, is uncertain. As in the preceding period, polynuclear leucocytes and lymphocytes migrate into or through the epithelium and may injure it in places, and lymphocytes may also collect in the connective tissue underneath the epithelial layer.

(b) *The uterine cervix.* In the uterine cervix the structure becomes more similar to that of the uterus. We find here a single layer of cylindrical epithelium, which rests directly on the connective tissue, although in places a second layer of flat cells may appear below the surface layer. In the beginning of the uterine cervix there may be observed some solid invaginations of epithelium into the connective tissue, while further towards the uterus typical glands appear. The papillary formations, characteristic of the middle cervix, become here less prominent, and the connective tissue of the mucosa becomes somewhat richer in cells, although it is not yet as cellular as in the typical uterine

mucosa. Mitoses are found in the cylindrical epithelium of the uterine cervix as in other parts of the cylindrical epithelium covering the cervix; likewise in the short glands of the uterine cervix rare mitoses may be seen, but in some cases they are lacking in the glands of the cervix even at periods when they are present in the uterine glands. However, it is of special interest that the predecidual proliferation which takes place in connective tissue and vessels of the uterine mucosa, approximately from the third to the sixth day following ovulation, does not occur in the uterine cervix, except perhaps in a small border area directly adjoining the uterus.

Uterus. We have previously described in detail the changes which occur in the uterus and mammary gland in the course of the sexual cycle, and we refer therefore essentially to our previous descriptions (1). We may recapitulate the principal events, as follows: In the first three days following ovulation the uterine surface epithelium is high cylindrical, and in the first two days mitoses are found in it. Also some small islands of vacuolar cylindrical epithelium resembling the uterine cervix epithelium may occur. Mitoses are seen after one day in the upper gland ducts and after two or three days they may extend to the middle portion of the gland ducts, but the gland fundi are as yet small. While in the connective tissue and capillaries of the mucosa there may at first still be some mitotic activity remaining from the oestrus period, after two and three days only a few mitoses are seen in the connective tissue and vessels of the subepithelial zone, indicating thus the beginning of the lutein phase. At this period some hyperemia may appear and occasionally some small hemorrhages are seen in the mucosa. A very active predecidual proliferation takes place in the uterine mucosa on the fourth and fifth day; the mitoses extend now to the gland fundi; but accompanying the proliferation in the subepithelial tissue and in the glands three, four and five days following ovulation, the mitotic proliferation in the surface epithelium ceases. Gradually towards the fifth and sixth days the surface epithelium becomes low, cylindrical, and mitoses in the glands likewise now are rare or altogether lacking. After six days there may still be occasional mitoses in the mucosa, but soon afterwards they cease entirely and degenerative processes occur in the predecidual cell layer. The glands also become small. At eight to

ten days after oestrus some mitoses may appear in the surface epithelium. The connective tissue of the mucosa is now in a resting state. Toward the end of the cycle the epithelium, glands and mucosa again begin to assume the oestral condition.

From the third day following ovulation to the end of the cycle the mammary gland is on the whole quiescent, although some rare mitoses may be found occasionally, but with the new period of heat, a temporary proliferation of the gland sets in anew.

Concerning the mechanism underlying the graded changes in the cervix. We see, then, that the proliferation which takes place under the influence of the hormone given off by the ovary at the time of oestrus shows a graded intensity which decreases in the direction from vagina to uterus. These findings might possibly be interpreted by the assumption that the proliferating epithelium of the vagina is mechanically pushed in the direction towards the cervix and into the vaginal cervix, and that thus the appearance of a graded proliferative activity is simulated, whereas in reality such a gradation does not exist. It can, however, be shown that such an interpretation would be incorrect. The gradual decrease in the number of mitoses which can be observed in passing in the direction from vagina to uterus, and which corresponds to the gradation in proliferation, is unfavorable to such an interpretation, as is also the graded change in the behavior of the keratin, which in the vagina and near the vagina is cast off earlier than at points higher up in the vaginal cervix, where it still remains adherent at a time when it has been cast off in the more distal areas. However, it is possible to decide this question definitely by interrupting the connection between the vagina and the cervix or between parts of the upper and lower vaginal cervix by applying a tight-fitting litgature around either the upper vagina or the vaginal cervix; such a procedure precludes a movement of the epithelium from the vagina into the cervix. We have carried out such experiments in a number of cases and have found that under these conditions the graded intensity in proliferation in the vaginal-cervical tract persists. If, however, the thread is applied in the cervix, a localized production of keratin is noticeable directly around the thread. We may then conclude that the gradation in proliferative activity in the vagino-cervico-uterine tract actually exists and is not merely

simulated through a mechanical pushing upward of the vaginal epithelium.

The same gradation in intensity of proliferation, associated with transitional conditions in structure in this area, which we observed under the influence of the follicular hormone given off in the course of the normal cycle, we also observed under experimental conditions, after administering a series of injections of follicular extract in guinea-pigs, and thus producing the signs of oestrus. Under these circumstances we see the same gradual decreasing intensity in the growth processes with which are associated the transitions in structure that we find in the normal cycle.

However, not only during the period of the normal cycle, but also in various other conditions have we observed the same correspondence between the structure of the different areas of the vagino-cervico-uterine tract and the growth processes under the influence of hormones. Thus in both hysterectomized and pregnant animals we found a resting state throughout the tract and a relative lack of growth processes; the conditions found in immature guinea-pigs or in those which are undernourished likewise sustain our conclusions. The changes taking place in the sex tract under these latter conditions, in so far as they have not yet been discussed previously, will be treated in a subsequent publication.

DISCUSSION AND CONCLUSIONS

Our observations prove that growth substances act on adjacent tissues in a graded way. The same amount of growth substance circulating in the body fluids induces in neighboring cells a response of graded intensity. This gradation corresponds to and is correlated with a certain gradation in the structure of the organs concerned. Furthermore, the responses obtained experimentally are identical with those observed during the normal cycle; it would seem, therefore, that in both cases they are produced by the same growth substances. If we inject follicular hormone in effective quantity twice a day in guinea-pigs, we find the vaginal epithelium proliferates and actively produces keratin. In the uterus, on the other hand, the changes, as far as proliferative activity is concerned, are relatively slight. There may be some edema and congestion and, here and there, we may observe

a connective tissue cell in mitotic division. In the cervix which joins vagina to uterus the proliferative conditions as well as the structural features are transitional between those found in the two adjoining organs and there is moreover a graded reaction; the nearer the portion of the cervix to the vagina, the more it reacts like the vagina at a particular period, although the reaction is always quantitatively weaker, until it reaches the neighborhood of the uterus, when it begins to show an activity and a structure approaching those characteristic of the uterus. There are two factors which might be concerned in this result. In the first place, it is conceivable that the gradation in intensity of proliferation is due to a gradation in the amount of substance taken up by the adjoining tissues, and, secondly, it is conceivable, even in case the tissues have taken up the same amount of growth substance, that their structure would cause them to respond to the action of the growth substance with a different degree of proliferation. It is also possible that a combination of these two factors is effective, and this latter assumption has the greater degree of probability, because it appears likely that the same factor which renders a tissue more or less adjusted to a hormone regulates the amount of this substance which is anchored to that particular tissue.

This is, as far as we know, the first instance in which there has been observed a gradation in the intensity of reaction to the stimulus of a hormone, corresponding to a gradation in structure of the reacting tissues. In regard to the interaction between growth substances and tissues, we can in general distinguish between two kinds of the former, namely, (1) those acting from a distance, as when a substance given off by one organ acts on another organ. Thus the substances given off by the corpus luteum and the follicular substance represent such agents. (2) Contact substances, among which may be included the organizator substances of Spemann. In all cases in which hitherto growth and differentiation were produced by such substances, a certain tissue either responded or did not respond. Under certain conditions the response was less intense than under other conditions; but to our knowledge no gradation in the response of adjoining tissues has ever been observed in either of these sets of reactions, such as we have observed in the case of the cervix. However, a certain relation may exist between the facts described

by us and the observations of Child and Hyman. These authors have observed that, in general, during regeneration or embryonal development or even in fully developed organisms, the most actively growing parts or organisms are those which are at the same time most sensitive to the effects of a diminution in the amount of available oxygen supply; and that gradients exist in which these two properties, namely growth and sensitiveness, increase or decrease in a corresponding manner.

As to the relation between the character of the tissues which enter into combination with the hormone, and the effectiveness of the hormone action, we must consider especially the intermediate part of the system, namely, the cervix. The distal part of the cervix, the vaginal cervix, is similar in structure to the vagina; but it differs from the latter in its gradually decreasing ability to react to the growth stimulus given off by the ovarian hormone. In the adjoining intermediate zone of the cervix, the epithelium undergoes changes which render it more similar in structure and behavior to the epithelial lining in the uterine cervix and to a similar type of epithelium which may occur in isolated areas here and there in the uterus. As a preparation for the gland formation which begins in the uterine cervix, we find in the intermediate, transitional zone of the cervix the development of epithelial recesses or crypts in which the epithelium is more solid; at the same time the formative conditions which are active here lead to the more marked development of papillæ. As an indication of the relationship between the epithelium of the intermediate zone and the vaginal epithelium, we may still find a slightly greater tendency to proliferation in the beginning of the intermediate zone. This tendency, however, soon ceases and the epithelium becomes unresponsive to the formative stimulus of the follicular hormone, and in this respect it resembles the uterine epithelium.

On the other hand, neither the connective tissue of the proximal portion of the intermediate cervix nor that of the uterine cervix acquires the ability to react to the stimulus of the corpus luteum hormone in a manner similar to the characteristic reaction which we established in the uterine mucosa. While thus the connective tissue of the proximal portions of the cervix does not become identical in character with the corresponding tissue in the uterus, we observe corresponding to a gradation in the

properties of the epithelium, a gradation in the character of the connective tissue, a more fibrous connective tissue being co-ordinated with the squamous epithelium of vagina and the potentially squamous epithelium of the vaginal or distal portions of the cervix and a more cellular connective tissue with the cylindrical or cuboidal epithelium of the uterus or the proximal portion of the cervix. However, at no period of the sexual cycle does the connective tissue, even of the uterine cervix, become as cellular as the connective tissue of the uterus.

Whenever the proliferative stimulus, acting on a responsive tissue, reaches a sufficient intensity, a transformation takes place of cylindrical epithelium, beneath which there may be a layer of flat cells, into squamous epithelium. The structure and metabolism of this epithelium is of such a kind that if the proliferation is rapid and the upper rows of the epithelium are thus raised up within a short time and removed a considerable distance from the blood vessels, the oxygen and food stuffs, the cells affected in this way undergo en masse a degenerative change which leads to the production of keratin.

In the case of the vagino-cervico-uterine tract, the epithelium shows certain structural differences. But there exist finer differences between adjoining portions which it is not possible to discern by ordinary distinctions based on structural characteristics, and for such differences fine gradations in the reactions permit a differentiation, where mere morphological criteria are insufficient. Similarly, it is the proliferative reaction, on the part of the connective tissue of the mucosa, to the hormone of the corpus luteum which enables us to differentiate between the connective tissue cells of the uterine mucosa and connective tissue cells of the cervix, vagina, Fallopian tube and serosa, although ordinary structural criteria of differentiation are lacking.

SUMMARY

1. An analysis of the actions of growth hormones on the vagino-cervico-uterine tract reveals a graded reactivity of the tissue to the stimulating effect of the hormone in the direction from vagina to uterus. The graded intensity of proliferation thus established corresponds to gradations in the structure of the tissue. This is, as far as we know, the first observation of a gradation of hormone action on contiguous parts of a tissue; it

is presumably due to a graded degree of reactivity of the tissues to the hormones as well as to a graded ability of adjoining cells to combine with certain hormones.

2. There are, associated with the intensities of proliferation of the epithelium, graded rapidities and intensities of transformation into keratin of the upper epithelial layers which are farthest removed from the source of oxygen and other foodstuffs, the process leading to the production of sheets of keratin and to an early casting off of these layers in the region corresponding to the greatest proliferative energy, a hyalinization of isolated cells taking place in the region corresponding to a diminished growth energy.

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THE IODINE CONTENT OF BLOOD IN ORDINARY GOITRES AND IN CRETINISM

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Since the adaptation of iodine determination, as described by Fellenberg and McClenden, interest has been stimulated in the determination of blood iodine content in man.

Veil and Sturm of Munich have contributed an excellent paper on the blood iodine content of human beings. Their work was done on normal and pathological individuals. They demonstrated the variability of iodine content under certain conditions; also the variability of blood iodine content in the same individual during summer and winter seasons, it being lower in the latter season.

That iodine is a constant and physiological element of the blood, is demonstrated by the fact that Veil and Sturm in the analysis of some 450 specimens found food iodine to be present in 100 per cent. The content in normal individuals is quite constant; also the variability of the different seasons. Besides many other pathological conditions, they also set forth the definite relation existing between blood iodine content in hypo- and hyper-thyroidism.

Taking a normal individual at late summer season and considering his iodine content at 13 milligrams per cent, they demonstrated that of the struma patient to be from 30 to 60 per cent lower than normal, showing only from 3 to 9 milligrams per cent, while in cases of Basedow's disease they found the content to be 21 to 70 milligrams per cent.

The contention that there is a definite relationship between the thyroid gland and iodine is substantiated to a certain extent by the experiments of Welch. His animal experiments were done at the Montana Agricultural College, Bozeman, Mon-

tana. In his conclusions he states that disturbance of function of the thyroid gland appears to be a cause of hairlessness in animals and that the enlarged thyroid glands are very deficient in iodine content. Iodine supplied to the female breeding stock during gestation is apparently effective as a preventative of goitre in the new born.

At the clinic of Bern it was thought that it would be of interest first to determine the iodine content of thyroid and peripheral venous blood, to ascertain whether or not a difference existed.

The method of determination employed was that of Fellenberg, under whose direction most of the following work was carried out in the laboratories of the Public Health Department of Bern.

In this paper, we shall not discuss the historical evolution begun by Robourdin in 1850, of the process of blood iodine determination, which has resulted in the present methods of Fellenberg and McClenden. This has been ably set forth in the papers of Veil, Sturm and Fellenberg. In this work the method of Fellenberg was followed precisely, and is but outlined as follows:

To 10 cc. of blood previously oxalated with 1 cc. of 2 per cent sodium oxalate solution, 1 gm. of KOH was added. This mixture was slowly ashed with constant stirring, using the usual precautions not to overheat the same and drive off some of the iodine content. The ash was then mixed with 10 cc. of distilled water and filtered. The remaining residue was again burnt quite thoroughly, and to this was added the filtrate which was slowly heated to dryness, finally heating to a red glow. After cooling, extraction was begun with alcohol. Six drops of potash solution plus 2 cc. of dilute iodine free alcohol was added and thoroughly rubbed, pouring the solution off into a platinum dish. Extraction with undiluted alcohol was repeated twice. Placing six additional drops of potash solution into the platinum dish, it was then placed upon the water bath and slowly steamed to dryness. It was often found necessary to repeat extraction with alcohol a second time owing to the large amount of residue remaining after heating on the water bath.

Determination of the iodine content was now done by both the titration and colorimetric methods. The residue in the platinum dish was dissolved in 1 cc. of distilled water and poured into a small test tube, to which was added one drop of a solution of dilute H_2SO_4 plus Na_2No_3, setting free the iodine, and 0.02 cc. of chloroform; then shaking thoroughly for a qualitative determination. The red violet chloroform drop was then compared with known standards. Proceeding next to the determination by titration, the solution used for the colorimetric findings, plus two washings of the platinum dish, were placed in an Erlenmyer flask, adding a small amount, approximately 0.5 cc. of bromine water and boiling until completely oxidized;

then after adding a kernel of potassium iodide and a drop of starch solution as an indicator, titration was done with N/250 $Na_2S_2O_3$ solution.

In the first group of experiments, 10 to 20 cc. of blood were taken from the basilic vein one-half hour before operation and the same amount from the thyroid veins at time of operation. One cc. of 2 per cent sodium oxalate solution was previously added to the container, the arm and operative field were prepared with picric acid. Patients were in the hospital 16 to 20 hours before operation, consequently the amount of iodine they would absorb by inhalation would necessarily be very small. The diet of the patients was inquired into, and also if they had been employing iodine in any form and when.

Glass stoppered bottles were employed for receiving the blood and not opened until after they were taken from the hospital to avoid any contamination with iodine.

The menstrual history of females was noted, for Veil has shown that during menstruation women have a hyperiodism. This is true also during pregnancy. Of the cases examined, none had iodine in any form for a period of one year previous to hospital admission. However, this is not extremely important, as it has been previously demonstrated that when iodine is ingested orally, blood iodine reached its highest point one and one-half hours after ingestion; nine hours after most of the excess iodine was out of blood stream; twenty-four hours after, the iodine content was just double the normal, and after forty-eight hours it was all eliminated, mainly through the urine.

Eleven cases of ordinary non-toxic goitres were examined with the following results. Controls were done in eight of the cases, with same results, as is shown in Table 1 and Figure 1.

From the results shown in Figure 1 the following observations can be emphasized:

(1) The thyroid gland must put out approximately as much iodine as it takes in; otherwise in a very short time it would either become overloaded or entirely free of iodine. At most it is thinkable that there are definite periods of storing and releasing of iodine. Our results show that such a regular change, perhaps daily variation, if it happens at all, occurs, at all events, in narrow limits.

TABLE 1

Patient	Peripheral Blood Milligrams Per Cent Iodine			Thyroid Blood Milligrams Per Cent Iodine		
	Colorimetric	Titration	Average	Colorimetric	Titration	Average
A. Z. B. 1883—Female. Duration 10 years. Struma-Nodosa.	10.	11.4	10.7	10.0	9.0	9.5
R. T. 1894—Female. Hemi-Thyroidectomy in 1913. Struma-Nodosa.	8.75	9.3	9.03	11.25	11.0	11.13
L. B. 1909—Female. Goitre since Puberty. Struma-Nodosa.	8.75	8.2	8.48	10.0	10.5	10.25
A. G. 1881—Female. Goitre since Puberty. Struma-Nodosa.	11.25	11.	11.13	10.0	11.2	10.6
A. N. 1876—Female. Goitre 10 years. Struma-Nodosa-Cystic.	8.75	9.4	9.08	7.5	8.0	7.75
E. B. 1874—Female. Goitre 20 years. Struma-Nodosa.	7.50	8.3	7.09	10.25	10.50	10.38
A. T. 1897—Female. Goitre 12 years. Struma-Nodosa.	8.75	8.0	8.38	10.0	8.0	9.0
L. M. 1893—Female. Goitre since Childhood. Struma-Nodosa.	11.25	11.0	11.13	10.0	11.0	10.5
R. A. 1906—Female. Goitre 6 years. Struma-Nodosa.	7.50	7.	7.25	8.75	8.0	8.38
M. G. 1900—Female. Goitre 5 years. Struma-Nodosa.	8.75	8.0	8.36	10.0	10.5	10.25
M. G. 1888—Female. Goitre 10 years. Struma-Nodosa.	11.25	11.0	11.13	10.0	12.0	11.0
Average	9.318	9.327	9.322	9.795	9.972	9.883

The fact that in our cases the venous thyroid blood contained as much iodine as that of the general circulation is still of more importance in other ways. It is theoretically possible that part of the iodine taken up by the thyroid gland is again given up to the blood stream by way of the thyroid lymphatic

system. However, this cannot be the case in accordance with our findings. The iodine component of the thyroid secretion, as far as we can conclude from two determinations, has, as a matter of fact, to come directly out of the thyroid gland into the venous blood entirely, or at least in greater part.

(2) In all of the cases, the blood iodine content was somewhat lower than the physiological normal, which would be expected in goitrous individuals. The examinations were also made during the winter season, which accounts for a lower iodine content.

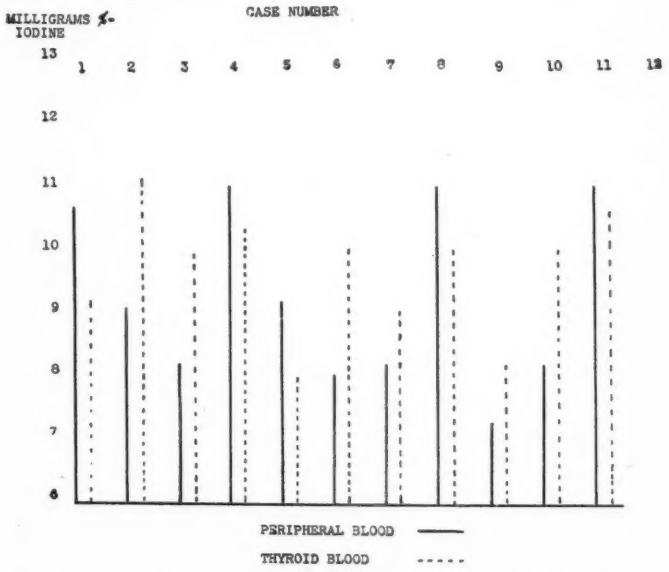

Figure 1. Milligrams per cent iodine in peripheral and thyroid blood.

(3) From these results it can be seen that there is but little variations between peripheral and thyroid blood iodine content. In six cases the iodine content of thyroid blood slightly exceeded that of the peripheral blood. In four cases the peripheral blood showed a slight increase over the thyroid blood. In one case the results were almost identical.

(4) The results seem to indicate:

(a) That the act of iodine intake and output of the thyroid gland occurs without great variations.

(b) That the iodine containing secretion of the thyroid gland arrives entirely, or for the greater part directly into the blood stream and not by the longer route of the lymphatic system.

In further study of the blood iodine problem, the peripheral blood of eleven cretins at Frienisberg, an institution near Bern, was examined, and also the peripheral blood of four normal individuals who were employees at this institution and living under the same conditions, having the same food, etc., as the cretins.

While much has been written on the etiology of cretinism, it is apparently the opinion of most writers that, while thyroid deficiency should predominate in our view of the classic conception of the disease, this is also accompanied by secondary deficiency in the other ductless glands. This is probably due to the lack of iodine in organic combination (thyroidin), for clinical experience has shown that the administering of thyroid gland relieves the symptoms and improves the patient, unless, of course, it is given after irreparable organic changes have taken place.

Knowing that the blood iodine content of cretins is from 50 to 70 per cent lower than normal, we thought it would be of interest to examine the blood of selected cretins and normal individuals at Frienisberg; then to feed or administer the both groups iodine and again examine the blood for its iodine content. After the first determinations were made each individual of both groups was given 0.1 gm. of potassium iodine in table form once daily for a period of seven days.

After a lapse of forty-eight hours to permit normal excretion of iodine, blood was again taken for examination to determine whether or not there was any variation in the iodine content of either group. Tables 2 and 3 show the results.

The striking difference between blood iodine content of cretins and normal individuals is readily seen by glancing at Tables 2 and 3 and Figure 2.

TABLE 2

CRETINS BEFORE KI ADMINISTRATION

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
C. K. 1884—Male. Typical Cretin, two nodules in struma size of tangernes.	6.25	5.4	5.83
J. M. 1882—Male. Twice operated upon—few nodules still present.	7.50	7.0	7.25
E. K. 1888—Female. Typical dwarf. Thyroid not palpable.	5.0	5.6	5.3
M. F. 1885—Male. Diffuse nodular goitre.	5.0	5.0	5.0
R. H. 1871—Female. Cretanoid features—large nodular goitre.	5.0	5.0	5.0
E. S. 1896—Male. Type of adult grown cretin, horse-shoe shaped goitre—nodular.	6.25	6.0	6.13
A. G. 1881—Female. Typical cretin features.	6.25	7.0	6.63
M. B. 1893—Female. Right lobe enlarged, fingers short but not clubbed.	7.50	7.0	6.63
E. A. 1890—Female. One large nodule—right.	6.25	6.00	6.13
C. A. 1880—Male. One large nodule in isthmus.	5.0	4.0	4.50
A. O. 1860—Male. Thyroid not palpable, features monkey-like.	7.50	7.60	7.55
Average	6.70	6.05	6.38

After administering 0.1 gm. of KI for a period of one week, blood was again taken from the both groups and examined with the results shown in Tables 4 and 5 and Figure 3.

By comparing these charts and figures with those just preceding, that is, before KI was administered, it demonstrates that the blood iodine content of cretins remains practically unchanged, while that of normal individuals is increased somewhat.

TABLE 3

Normals With No Clinical Evidence of Goitre Before Iodine Administration

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
H. W. 1886—Male. At institution 2 years.	12.50	13.65	13.08
H. B. 1880—Male. At institution 4 years.	13.12	14.25	13.68
G. L. 1888—Male. At institution 2 years.	11.25	11.0	11.13
L. S. 1889—Female.	13.75	12.48	13.11
L. E. 1894—Female.	14.38	14.76	14.57
Average	13.0	13.23	13.12

TABLE 4

Cretins After KI Administration

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
C. K. 1884—Male.	6.25	6.5	6.38
J. M. 1882—Male.	6.75	7 4	7.08
E. K. 1888—Male.	6.25	6.6	6.43
M. F. 1885—Female.	5.0	6.2	5.6
R. H. 1871—Female.	5.6	5.14	5.37
E. S. 1896—Male.	7.50	7.4	7.45
A. G. 1881—Female.	7.0	6.5	6.75
M. B. 1893—Female.	6.25	6.4	6.33
E. A. 1890—Female.	6.3	6.5	6.4
C. A. 1880—Male.	5.6	6.0	5.8
A. O. 1860—Male.	6.9	6.6	6.75
Average	6.36	6.48	6.42

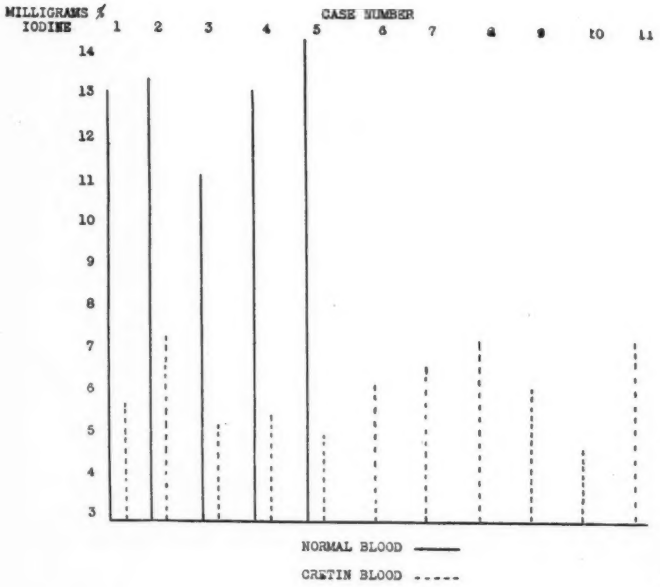

Figure 2. Milligrams per cent iodine in normal and cretin blood.

TABLE 5

Normals After KI Administration

Patient	Colorimetric Milligrams Per Cent Iodine	Titration Milligrams Per Cent Iodine	Average Milligrams Per Cent Iodine
H. W. 1886—Male.	16.25	17.4	16.83
H. B. 1880—Male.	15.4	14.2	14.35
G. L. 1888—Male.	15.62	16.0	15.81
L. S. 1889—Female.	14.6	14.5	14.55
L. E. 1889—Male.	15.0	15.5	15.25
Average	15.19	15.52	15.36

CONCLUSIONS

1. The blood iodine content of cretins is persistently fifty to seventy per cent lower than that of normal individuals when on an average diet.

2. The blood iodine content of cretins is practically unchanged by the administration of iodine in the form of potassium iodide, taking blood forty-eight hours after stopping the potassium iodide to allow for normal excretion.

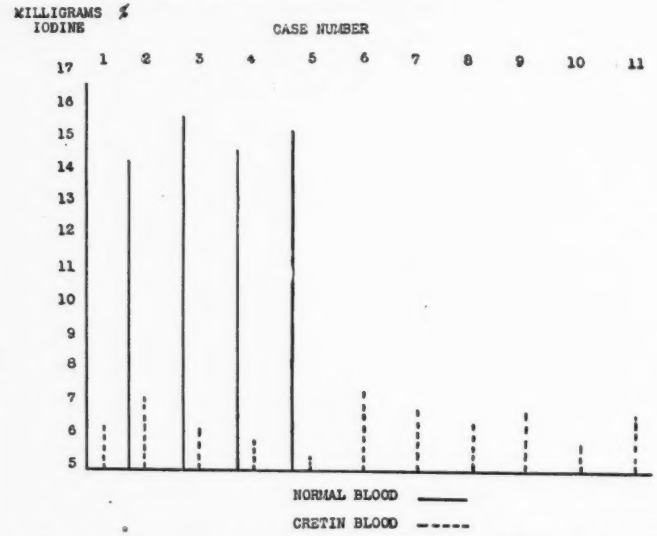

Figure 3. Milligrams per cent iodine in normal and cretin blood after KI administration.

3. The iodine content of a normal individual's blood is somewhat and undoubtedly only temporarily increased after the administration of potassium iodide, allowing the same amount of time for normal excretion.

4. This apparently shows that the cretin retains practically none of the administered iodine, while the normal individual increases his blood iodine content a small amount, but probably only for a short period of time. If the blood had been taken seventy-two or ninety-six hours after ceasing administration, it most likely would have shown no increase over the normal amount.

5. These findings tend to show that the cretin must excrete iodine at a more rapid rate than the normal individual. His powers for retaining iodine, even for a short period of time, are practically nil.

6. According to Veil and Sturm in comparing the iodine content of the Basedow patient, the normal individual, the ordinary goitre patient and that of the cretin, and in accordance with our determinations, we may say that the level of the iodine content is regulated by the organism automatically, according to the degree of function of the gland. In our determinations this regulation would be rather disturbed only for a short period of time by artificial administration of iodine. Thus exists the same self regulation of blood iodine, as the other indispensable elements of metabolism.

With these facts in hand it was desired to determine more conclusively that iodine is excreted by cretins at a more rapid rate than normal. We had a congenial and more or less cooperating cretin who resided at the clinic for demonstrating purposes as being a typical example. Notwithstanding his intellectual deficiency he was quite clever in that each time we desired to withdraw blood from his arm he demanded a package of cigarettes, and promises of tomorrow he would not listen to.

We took this cretin and selected another patient in the same ward who was being treated for a varicose ulcer of the lower extremity. The cretin was admitted to the hospital on October 15th, 1924, and the patient with the varicose ulcer on June 24th, 1926. Both patients received the same amount of potassium iodide and twenty-four hour urine specimens were examined for iodine content.

Dealing with a larger quantity of iodine, Dr. Fellenberg thought it best to modify his original method of determination, and the approximate alterations were as follows:

To 5 cc. of urine was added 2.5 cc. K_2CO_3 solution and sufficient aqua distillata to make 50 cc. One cubic centimeter of this solution equalled 0.1 cc. of urine, which was put into a platinum container and heated on the water bath until vaporized. This was then heated over a flame until the residue was white. After cooling, the residue was dissolved in about 1 cc. of distilled water and placed in an Erlenmeyer flask. The residue was extracted with distilled water three or four times to insure that all the iodine was in solution. One drop of methyl orange was added as an indicator and the solution acidified with dilute hydrochloric acid, adding three drops more of hydrochloric acid to insure acidity. One cubic centimeter of bromine

solution was then added and the solution boiled down to approximately 5 cc. Then we proceeded to determination by titration, as previously referred to.

The results of the comparison of iodine excretion in the urine of a cretin and normal control is shown in Table 6.

TABLE 6

J. G.—1872 Cretin. Admitted to hospital 10–15–24.				E. G.—1884 Varicose Ulcer. Admitted to hospital 6–24–26.			
Date	Amount of KI Administered	24-Hr. Urine	Grms. of KI Excreted	Date	Amount of KI Administered	24-Hr. Urine	Grms. of KI Excreted
6–30–26	0.25	1400 c. c.	0.12	6–30–26	0.25	2400 c. c.	0.08
7– 1–26	0.5	1450 c. c.	0.34	7– 1–26	0.5	1640 c. c.	0.21
7– 2–26	1.0	1830 c. c.	0.68	7– 2–26	1.0	2000 c. c.	0.43
7– 9–26	0.25	1600 c. c.	0.09	7– 9–26	0.25	2100 c. c.	0.09
7–10–26	0.5	1750 c. c.	0.37	7–10–26	0.5	1810 c. c.	0.26
7–11–26	1.0	1920 c. c.	0.52	7–11–26	1.0	2200 c. c.	0.48

On July 2nd, 1926, 20 cc. of blood was taken from the median basilic vein of each patient, before the administration of the morning dose of KI on the 3rd day. This was titrated. The blood iodine content of J. G., the cretin, was 20.52 milligrams per cent, while that of E. G., the normal, was 32.46 milligrams per cent.

CONCLUSIONS

The result of this experiment tends to show that cretins excrete iodine through the urine at a slightly more rapid speed than normal. In the six determinations, each of which was repeated three times to insure accuracy of results, the cretin excreted more iodine than the control subject; on the same given amount, in only one determination, the amount excreted was the same.

The blood determination, taken during the course of the experiment, again shows the interesting fact that during the same amount of iodine administration, the blood iodine content of a normal individual is appreciably higher than that of the cretin.

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GRAVES' DISEASE REDEFINED

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Since neither exophthalmos nor goiter need be present in otherwise typical instances of Graves' disease, the term exophthalmic goiter as a synonym is confusing and a hindrance to progress in diagnosis and treatment. In my series of 3,343 cases recently reported (1) there was no tangible thyroid enlargement in approximately 20 per cent, and in 15 per cent no exophthalmos existed. In 9 per cent neither exophthalmos nor goiter was observed. The percentage thus atypical would be found considerably greater were it possible to include the many cases in general practice that are undiagnosed because of the absence of both exophthalmos and goiter.

Some time ago (2) I suggested that were Graves' disease removed from the classification of goiter and placed in the category of constitutional affections, the thyroid gland would cease to be incriminated as the etiological factor. The removal of the burden of causation from the thyroid is a procedure with which most investigators are in accord.* It would also assist in keeping the busy practitioner's mind more alert for the recognition of atypical forms of the disease and would result in a reduction in the number of cases misdiagnosed or recognized only after considerable damage to circulatory and other vital structures has occurred.

Those who see many sufferers from Graves' disease observe that thyroid swelling does not precede but follows such significant signs and symptoms as tremulousness, changes in behavior and emotionalism, undue moisture of the skin, a feeling of unusual warmth, palpitation and dyspnea, fatigability, loss in weight, and an unaccountable tendency toward the speeding up of all physical and mental functions. Swelling of the thyroid, if it occurs at all, is a later event in the evolution of this affection. This would seem to justify the view that the swelling is a

* The use of such terms as hyperthyroidism, thyrotoxicosis and toxic goitre, implying thyroid causation of the syndrome, are likewise misleading as synonyms of Graves' disease.

defensive reaction against causative toxins originating elsewhere in the body.

In carefully taken family histories of these patients one is struck with the probability that the disease is the culmination, usually through a psychic trauma as the exciting cause, of a lifelong, frequently congenital predisposition to the malady. Commonly there is elicited the information that one or more members of the family are or have been afflicted with nervousness, diabetes mellitus, Graves' disease, or some other condition of nervous or endocrine causation. In the previous medical and personal history goiter is almost never stressed by the sufferer; it is the nervous factors that are brought fully to the fore and complained of as having existed over a period of years.

Prolonged observation of these individuals impresses one with the constancy of three clinical facts:

1. Graves' disease in its active stage* invariably presents an abnormally high basal metabolic rate. Hence we might safely conclude that whatever its etiology the disease is a *catabolic* disturbance.

2. Almost never does a patient with Graves' disease fail to present marked disturbances of the central and peripheral nervous systems. There is a universal speeding up of nerve function; the threshold of emotional reaction is shortened so that unusual behavior of the patient, asserting itself especially in excitability, is one of the earliest symptoms noted. Autonomic imbalance is evidenced by flushing of the skin, dermographia, sweating, and the many signs associated now with sympatheticotonia, now vagotonia, again a combination of the two with one or the other predominating. Hence we are also justified in concluding that the disease is largely to be regarded as one of *nervous dysfunction.*

3. The endocrine aspect of Graves' disease is of decided interest. Irrespective of whether the thyroid gland is disturbed qualitatively, quantitatively, or both, it is fairly well established that the disease is not *due* to hyperthyroidism. The majority of observers believe dysthyroidism to be a constituent of Graves' disease, since the *nature* of the thyroid hormone appears to be abnormal. Parathyroid hyposecretion appears probable because of the tremor and low blood calcium content characterizing the

* During a marked remission of the disease there may be no abnormal metabolic rate. In this paper we are discussing Graves' disease in its *active* stages.

disease. The commonly observed thymus hyperplasia justifies the belief that this organ is usually in a state of hypersecretion. The lowered carbohydrate tolerance is evidence of hypofunction of the internal secretion of the pancreas. Again, gonadal insufficiency is indicated by the commonly observed amenorrhea and other menstrual disturbances, and sterility. Less certainly, but nevertheless with reason, we might state the suprarenal medulla to be in a state of hyperfunction and the cortex in hypofunction; also that the posterior pituitary is in a state of hypofunction, while the anterior portion of this gland is in hyperfunction. Hence to infer that Graves' disease is an affection of *endocrine dysfunction* appears reasonable.

From the above paragraphs we might state that whatever the cause of Graves' disease, it asserts itself clinically as a *catabolic neuro-endocrine dysfunction.* It would thus appear that we are in position to redefine this affection as follows:

Graves' disease is a chronic, rarely acute, neuro-endocrine dysfunction characterized by an increased basal metabolism, loss in weight, tremor, emotionalism, persistent afebrile heart hurry, weakness, dermographia, and usually (not constantly) by hyperplasia of the thyroid gland and by exophthalmos.

CONCLUSIONS

The presence of neither exophthalmos nor goiter is imperative for the recognition of Graves' disease, hence the synonym "exophthalmic goiter" is confusing in the diagnosis of this affection.

The adoption of the above definition of Graves' disease is urged with the hope that it would assist in the elucidation of the nature of this perplexing clinical entity.

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OBSERVATIONS ON THE ORAL ADMINISTRATION OF THE ŒSTRUS PRODUCING AUTACOID

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It is established that the œstrus producing autacoid, if given in adequate dosage subcutaneously, intramuscularly, intravenously or intraperitoneally, will produce the phenomena characteristic of œstrus in oöphorectomized animals. Hitherto observers have been of the opinion that this autacoid is inactive when taken by the mouth. This view the writer was not inclined to accept until relatively large doses of the autacoid had been exhibited orally in laboratory animals. It was therefore decided to administer the autacoid in large doses to oöphorectomized albino rats with the object of producing, if possible, the vaginal smear changes characteristic of œstrus.

EXPERIMENTAL CONSIDERATIONS

Virgin female albino rats weighing between 90 and 150 grams each were chosen for the experimental work. It has been shown that rats may, in some instances, remain in anœstrus for weeks at a time, even where the ovaries have been untouched. In order to exclude this type of rat from the series under observation, a dose of 25 rat units of a known active preparation of the autacoid was given subcutaneously in each instance before oöphorectomy was performed, and the capacity for going into œstrus observed. In none of the rats used for this investigation, however, did failure to go into œstrus occur.

With regard to the technique used in the oöphorectomization of this series of rats, some consideration was given to this matter, since it has been observed that œstrus cycles have recurred in some apparently oöphorectomized rats some weeks following operation; post-mortem examination, however, invariably yielding evidence that fragments of the ovaries had been left behind.

It has been suggested that seven to ten days should elapse after oöphorectomy before the animals are used for testing purposes, during which time vaginal smears should be examined daily. It will be obvious that this period would have to be much prolonged to exclude all possibility of any ovarian tissue being left behind. Apart from the fatigue which such a procedure would entail, I have found that some of my animals became insensitive to adequate injections of the autacoid some four weeks following oöphorectomization, possibly due to atrophic changes taking place in the vagina. In one rat atrophy was so marked five weeks after oöphorectomy had been performed that I was unable to insert a medium sized probe into the vagina.

Bearing the foregoing points in mind, it was felt that the only adequate way of making certain that the ovaries had been completely removed was to freely lay open the abdomen and take special precautions to remove all ovarian tissue.

OPERATIVE TECHNIQUE

The rats were anæsthetized with ether and, taking all aseptic and antiseptic precautions, the abdomen was freely laid open by a long mid-line incision.

The intestines were turned out and the uterine horns clearly exposed in their whole length, from the vaginal vault to the ovaries on each side. Having identified the ovaries, these were removed, having first clamped the broad ligament and uterine horn for half an inch distal to the ovary. No ligatures were required or applied.

It was possible, in this way, to get an exposure of the ovaries equal to that obtainable in a post-mortem examination. In spite of the severity of the procedure, I had no operative mortality and the rats appeared to be quite well the day following operation.

The oöphorectomized rats were divided into groups of six and allowed to remain for between seven and ten days before being used for testing purposes.

ADMINISTRATION OF THE ACTIVE PRINCIPLE

It has been clearly demonstrated that the œstrus producing material can be readily obtained from whole ovaries, and it was decided to feed the rats on these.

Sows' Ovaries. (Experiment I.)

The ovaries used were seen to contain numerous active follicles and were therefore presumed to be obtained from animals in full sexual activity.

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	---	0	0	0	0	0	---	---	0

--- No observation.

Twelve of these ovaries were given to 6 rats in one cage. The ovaries proved appetizing and were disposed of within 24 hours. Daily vaginal smears were taken and a search made for the cell changes characteristic of œstrus.

At the end of the 7th day of administration of the ovaries no rats were found to have shown œstral changes during this period. Final smears were taken on the 10th day with negative results.

Sows' Ovaries. (Experiment II.)

Day.....	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus.....	---	---	0	2	2	1	0	---	---	0

In the second experiment, using a new batch of oöphorectomized rats, 3 sows' ovaries were coarsely chopped up and given daily for 4 days.

Care was taken to mop up the follicular fluid, which escaped in the chopping-up process, with bread, this bread being given to the rats in addition to the ovaries.

Daily smears were taken from the vagina as in Experiment I.

On the 4th day 2 rats were found to be in œstrus.

Daily examinations were made for a further 3 days and a final one on the 10th day of this experiment; no more rats, however, went into œstrus.

This experiment seemed promising, hence it was decided to place 6 rats in separate cages and to feed them daily on the maximum quantity of ovarian tissue which they could consume until they all showed the phenomena of œstrus.

Horses' Ovaries. (Experiment III.)

It was decided to use horses' ovaries for this experiment as they are very much larger than those taken from sows.

The ovaries chosen for administration appeared to be rich in follicles.

Day	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus	---	---	0	1	4	4	6	---	---	---

The amount of ovary consumed per rat was not weighed, but roughly consisted of one-third to one-half an ovary daily.

With this method of feeding one rat was found to be in œstrus on the 4th day, 4 rats on the 5th day, 6 rats on the 7th day of feeding. The feeding was then discontinued.

As a further check in this series the rats were killed and a search made for ovarian tissue with, however, negative results.

QUANTITATIVE EXPERIMENTS

Having demonstrated that ovarian feeding could be successful in the production of œstrus it was felt that some quantitative work would prove useful.

The product used in this work was the experimental substance "Estrogen" placed at my disposal by Messrs. Parke, Davis & Co.

This product, which is obtained from the placenta, is issued as containing 25 rat units per cc., as assayed by the formula:

$$\text{Rat Units per cc.} = \frac{W}{140\ Q}$$

W represents the weight of the rat in grams.

Q represents the minimum number of cubic centimetres of the preparation which causes typical œstrus in any rat used in the test.

Samples were taken from the batches of ampoules which were supplied for this work and tested for activity. One batch proved totally inactive, but in the remainder the activity was found to be as indicated. The apparent irregularity in the activity of this particular product has occurred in specimens of the œstrus producing autacoid prepared by myself on a small scale and, furthermore, has been found to occur in all samples of commercial products which I have tested.

I have found the substance tested to be either totally inactive or active to the extent anticipated or indicated; this fact points, I think, to the œstrus producing autacoid, being somewhat unstable in nature.

Incidentally, the work of Bugbee and Simond (1926), in which they report experiments which demonstrate that the dose of the œstrous producing autacoid should vary according to the body weight of the rat, was confirmed.

Furthermore, opportunity was taken of controlling the specificity of this substance by giving control injections of acetone and alcohol extracts of brain and testicular tissue. No œstrus was produced by either of these substances.

Estrogen Feeding. (Experiment IV.)

Day	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus	---	0	5	6	---	---	---	---	---	---

Five hundred rat units were dissolved in the animals' drinking water which was common to all 6 rats under observation.

Oestrus changes were detected in 5 rats on the 3rd day of the experiment and 6 rats on the 4th day.

Estrogen Feeding. (Experiment V.)

Day	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus	---	0	1	2	0	0	---	---	---	---

Three hundred rat units were administered in a similar way to that used in experiment IV and utilizing the same rats. An interval of 7 days elapsed between this and the previous experiment.

Three rats only in this group went into œstrus, one on the third day and 2 on the fourth day of the experiment.

Estrogen Feeding. (Experiment VI.)

Day	1	2	3	4	5	6	7	8	9	10
No. of rats in oestrus	---	0	0	0	0	0	---	---	---	---

One hundred fifty rat units were administered in a similar way to that adopted in Experiments IV and V.

The results in this series were entirely negative over a period of 5 days' observation.

DISCUSSION

In experiments IV, V and VI between 300 and 500 rat units proved necessary to produce œstrus in 6 observed rats when the product was administered by the mouth.

The combined weight of the rats used in these experiments amounted to 909 grams, giving an average weight of 151.5 grams per rat.

Taking the mean of the figure 300 and 500, *i. e.*, 400, as being the number of rat units necessary to produce œstrus in 6 rats of

an average weight of 151.5 grams each, we obtain the figure of 66.6 as being the number of rat units necessary to produce œstrus in a rat of 151.5 grams, the product being administered orally.

Utilizing the formula of standardization which I have mentioned previously, the amount which should prove necessary to produce œstrus in a rat of 151.5 grams would be 1.08 rat units. Oral administration, however, required 66.6 rat units.

It would appear therefore that the ratio of activity of the oral method of administration to the subcutaneous is 1:61.6.

SUMMARY

(1) The œstrus producing autacoid is active if administered by the oral route in adequate dosage.

(2) The dose required is some sixty times larger than that which is necessary when the hormone is administered by injection.

I am particularly indebted to Professor Swale Vincent for providing me with laboratory facilities in connection with this work, also for much help and constructive criticism in the conduct of the experimental work.

I also wish to acknowledge the courtesy of Messrs. Parke, Davis & Co., in providing me with adequate supplies of their experimental product, Estrogen, used in this investigation.

The expenses of the investigation were in part defrayed by a grant* to Professor Swale Vincent, which he kindly diverted to this purpose.

* From the British Association (Ductless Glands Committee).

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THE EFFECT OF DUODENAL SECRETIN UPON THE SECRETION OF INSULIN BY THE PANCREAS

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In a previous work (Nóvoa Santos, Criado and Barreiro, 1924), it was shown that intravenous injections of duodenal secretin into both men and lower animals produced in all cases a marked hypoglycemia. Independently of our work, Penau and Simonnet (1925) came to the same conclusions. Criado, working in my laboratory has later confirmed these results, the data of which will soon be published in detail. Some of the results obtained are given in the accompanying tables.

A comparative study of the action of insulin and secretin upon blood sugar shows that the effect of insulin is the more intense. The following data show this effect:

BLOOD SUGAR IN DOGS INJECTED WITH 1 CC. OF SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.15 per 1,000	1.5	1.15	1.00
II.	1.15 per 1,000	1.00	0.92	0.92
III.	1.32 per 1,000	0.82	0.80	0.60
IV.	1.39 per 1,000	1.17	1.17	1.06
V.	1.35 per 1,000	1.39	1.60	...
VI.	1.18 per 1,000	1.50	1.03	1.50

RABBITS INJECTED WITH 1 CC. OF SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.00 per 1,000	0.85	0.95	0.95
II.	1.20 per 1,000	1.02	0.90	0.90
III.	1.86 per 1,000	1.00	0.95	1.05
IV.	1.17 per 1,000	1.09	1.03	1.10
V.	1.23 per 1,000	1.10	1.02	1.05
VI.	1.64 per 1,000	1.64	1.70	1.21

MEN INJECTED INTRAVENOUSLY WITH 1 CC. OF SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.25 per 1,000	1.21	1.14	0.80
II.	1.14 per 1,000	1.14	1.39	0.89
III.	1.07 per 1,000	0.96	0.64	0.75
IV.	1.28 per 1,000	1.21	0.80	1.28
V.	1.00 per 1,000	0.89	0.82	0.75
VI.	1.10 per 1.000	0.53	0.71	0.71

RABBITS INJECTED WITH 1 CC. OF SECRETIN AND 10 UNITS OF INSULIN

SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.20 per 1,000	1.02	0.90	0.90
II.	1.17 per 1,000	1.09	1.03	1.10
		INSULIN		
I.	1.25 per 1,000	1.00	0.86	0.64
II.	1.20 per 1,000	0.64	0.60	0.64

DOGS INJECTED WITH 1 CC. OF SECRETIN AND 10 UNITS OF INSULIN

SECRETIN

	Before Injection	15 Minutes After Injection	30 Minutes After Injection	1 Hour After Injection
I.	1.15 per 1,000	1.15	1.15	1.00
II.	1.32 per 1,000	0.88	0.80	0.60
		INSULIN		
I.	1.03 per 1,000	0.58	0.82	0.90
II.	1.42 per 1,000	0.50	0.30	0.30

In our previous work we advanced the hypothesis that this hypoglycemic action of secretin was perhaps due to its contain-

ing some active substance, such as the internal secretion of the pancreas. We have, however, no data that would confirm such a supposition. Penau and Simonnet do not think that the hypoglycemic reaction is caused by the internal secretion of the pancreas, since in the depancreatized dog this hypoglycemic action of secretin is still obtained, as in the normal animal. Lambert and Hermann (1925) also have reported that the variations in blood sugar caused by secretin persist after the extirpation of the pancreas. In two pancreatectomized dogs we have been unable to find any significant variations in blood sugar following the injection of secretin. In one of these animals the fasting blood sugar was 2.78 per 1000. Fifteen minutes after the injection of 1 cc. of secretin the blood sugar was 3.25. Half an hour after the injection the blood sugar was 3.03; an hour after the injection, 3.03. In the second animal the fasting blood sugar level was 3.45 per 1000. After the injection of 2 cc. of secretin, in fifteen minutes the blood sugar was 3.45; in half an hour, 3.64; in an hour, 3.57. Other experiments gave similarly negative results.

In spite of these results, it is not believed that the problem is yet definitely settled. These data are given in view of the work reported by Freud and Saddi-Nazim (1926) in which they agree with a point of view expressed by me that duodenal secretin has an activating influence upon the pancreatic islands. Freud and Saddi-Nazim have shown that in a half hour after the introduction into the duodenum of 50 to 100 cc. of 5 per cent HCl, the blood sugar content is diminished. This condition persists for an hour, and may be obtained even after the destruction of the digestive acinar portion of the pancreas by ligation of the duct. The conclusions reached by these workers and by Gley (1926) are that the duodenal secretin produced by the introduction of HCl into the duodenum, stimulates the production of insulin, but that the hypoglycemia is due to the secretin produced and not to the insulin. Hence, their interpretations agree with the results of the experiments of Simonnet, Lambert and Hermann and with our colleagues.

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A SEX DIFFERENCE IN INTESTINAL LENGTH AND ITS RELATION TO PITUITARY SIZE

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Clinical observations have indicated that hypersecretion of the anterior lobe of the pituitary gland is associated with splanchnomegaly. Cunningham, according to Barker (1), reported a case in which the length of the small intestine was doubled. In the human, however, we are quite without data concerning intestinal length in the normal male and female; and, apparently, the weight of the pituitary is available for only four normal men and one woman (2). Here the female pituitary was larger, in the ratio 1.5:1.

In rats the pituitary of the female is definitely known to be larger than that of the male. For Albino, the data of Hatai (3) and of Jackson (4) show values of 8.9 and 15.8 mgms. in males and females, respectively. Addison and Adams (5) have further shown that though the female *pars nervosa* is somewhat larger, the female *pars anterior* is more than double that of the male. From the wild Norway rat Hatai (6) obtained data from 31 males and 17 females. The body weight of the males was somewhat greater (males, 252 grams; females, 227 grams), but in them the hypophysis averaged smaller (8.0:8.4 mgm.). On the other side of the present problem—that of intestinal length—no measurements are available for the rat.

The data of this communication make it entirely clear that female Ring doves have longer intestines than the males. And in this family of animals some data on pituitary size are at hand. McCarrison (7) has earlier concluded that "in healthy common pigeons the pituitary is considerably heavier in the females than in the males." Altogether, McCarrison weighed 69 pituitaries. In healthy males and females he got averages of 5.3 and 5.9 mgms. (19.3 and 22.1 mgms. per kgm. body weight); from birds with dietary deficiency he obtained nearly similar values (5.8 and 6.3 mgms.; or, 19.6 and 22.4 mgm. per

kgm. body weight). These data are probably insufficient for a valid determination of this point; we can now, however, add a few weighings on pituitaries of similar common pigeons which tend to confirm this sex difference in pituitary size. It thus results that the doves and pigeons provide us with data definitely showing that the females have longer intestines (doves), and that this is probably associated with larger pituitaries (pigeons).

TABLE 1

Length of Intestine in Five Racial Groups of Ring Doves and Ring Hybrids

Race or Group	Healthy or with Ascaridia	No.	Average Body Weight Grams	Average Intestinal Length Centimeters	Seasonal Mean	Per Cent* Excess in Females
			MALES			
Ring A.....	Healthy ...	78	152	49.75	49.9	
	Ascaridia ..	78	158	50.7	50.45	
Ring B.....	Healthy ...	49	156	55.55	55.95	
	Ascaridia ..	20	151	57.05	57.35	
Ring C.....	Healthy ...	26	166	50.5	49.6	
	Ascaridia ..	15	169	52.4	52.1	
Group 4.....	Healthy ...	171	159	52.6	52.4	
	Ascaridia ..	59		54.6	54.8	
Trispecific ...	Healthy ...	53	162	49.6	49.6	
	Ascaridia ..	27		52.6	53.9	
			FEMALES			
Ring A.....	Healthy ...	70	150	51.35	50.45	3.2
	Ascaridia ..	76	150½	52.75	53.25	4.0
Ring B.....	Healthy ...	32	149	57.4	57.45	3.3
	Ascaridia ..	21	152½	60.85	61.45	6.7
Ring C.....	Healthy ...	13	164	53.9	54.4	13.0
	Ascaridia ..	13	162	60.0	58.9	14.6
Group 4.....	Healthy ...	157	155	54.6	55.4	3.9
	Ascaridia ..	121		58.1	57.5	6.8
Trispecific ...	Healthy ...	38	154	53.9	54.1	8.7
	Ascaridia ..	40		56.9	54.9	8.2

In Table 1 the intestinal length is given for males and females of five "groups" of ring dove *(Streptopelia)* races. The races of "Group 4" contain traces of another genus. The "trispecifics" are contaminated with *St. douraca.* Birds with

*The average for each race was first obtained (12 races in "group 4"); an average for the group, as listed, then found.

disease other than ascariasis are entirely omitted; birds bearing Ascaridia are classified apart from the healthy animals. Five racial groups are listed. In obtaining the figures tabulated the two or more races which form each racial group were separately tabulated, and indeed on the basis of season—since the possibility of seasonal change exists. Both the average and the seasonal mean for intestinal length was calculated. Each race within the group—though represented by unequal numbers of individuals measured—was made coequal with the others in deriving the figures as tabulated. The measurement is for that part of the intestinal tract lying between the gizzard and the anus. The birds were killed by decapitation. Shortly after all intestinal movement had ceased, the abdominal cavity was opened; the intestine was then removed; the mesenteric folds enforcing all curvatures were torn apart; and finally, the intestine laid (with as nearly uniform stretching as possible) on a horizontal meter-stick for measurement. It is important to note that all these data are from sexually mature animals (6-30 months).

In all of the 10 comparisons afforded by the table the female intestine exceeds that of the male in length. This also despite the fact that the body weight of the males exceeds the weight of the females by about 2 per cent. It is further shown that ascariasis is associated with increased length of intestine in both sexes. The data were obtained from 377 healthy, and 199 ascariasis males; and from 310 healthy, and 271 ascariasis females. These data from 1157 birds leave no doubt that a sex difference in intestinal length exists in adult ring doves—the female intestine is both absolutely and relatively the longer. With body weight considered the difference averages 5-10 per cent.

It should here be noted that we have also obtained several hundred measurements of intestinal length in various races of common pigeons. On account of wide racial differences there these must, however, be treated as several different groups. A still greater source of trouble is found in the fact that in these pigeons an unrecognized disease—marked in its later stages by great emaciation and extreme intestinal length—is at times rather prevalent in these forms. Early stages of this disease

are not definitely recognizable but are probably accompanied by abnormal intestinal length. These facts introduce elements of uncertainty into measurements made on intestinal length in our common pigeons. In Table 2, however, we give the data obtained from those presumably healthy birds whose pituitaries were weighed. The females there also show the greater intestinal length.

The dissection and weighing of the hypophysis of pigeons is a rather difficult thing, and reliable weights can be obtained only after considerable practise. The task is particularly difficult in ring doves in which the body size is only about half that of common pigeons. In the two groups we have made about 100 weighings, but rather more than half of these were made on glands from heads preserved in formalin. Comparison has shown that these latter are modified and not at all comparable with fresh weights. In Table 2 we give the fresh weights obtained on healthy common pigeons (14 males and 12 females). It will be seen that the average pituitary weight obtained from females is slightly greater, and that when body weight is taken into account, it is considerably greater (22.6:19.6 mgm. per kgm.). These figures are closely similar to those obtained by McCarrison and cited above. We are in-

TABLE 2

Pituitary Weight in Common Pigeons (*Columbia domestica* var.)

Sex—	Number	Age Months	Body Weight Grams	Length Intestine cms.	Pituitary Weight* Milligrams	Pituitary Per Kilo Body Weight
Males	14	24.0	361	94.4	7.06	19.6
Females	12	19.5	316	100.2	7.13	22.6

debted to Dr. Gertrude H. Transeau, of Columbus, Ohio, for these particular weighings.

Among doves and pigeons it is therefore clear that the females have the longer intestines, and it is made highly probable that in these forms they also have larger pituitary glands. The partial data on these two points now available in the human and

the rat are in full accord with this result. The longer intestine of the female dove is also in interesting agreement with the larger liver and spleen which Riddle (8) has recently shown to characterize the females of this species.

It remains to point out that in a recent paper dealing with the *growth* of organs and organ systems in White Leghorn fowls Latimer (9) does not find the sex differences in pituitary and intestine which we have just described in the pigeon. Autopsies were made on 100 fowls whose ages ranged from hatching to maturity. The results were presented in the form of curves only, so that direct numerical comparisons are scarcely possible. The entire digestive tube was *weighed*—its length not taken—and on the basis of these weights "there is no apparent sex difference." Latimer also weighed apparently about 90 pituitaries of these chicks. Most of these weighings were on immature birds. It is concluded that "the data on the chick show no appreciable sex difference when the weights are plotted against the body weight. If there is any difference at all it is rather in favor of a heavier male hypophysis." The numbers involved, though by no means negligible, are not large. It is particularly notable, however, that few measurements were made on *adult* fowls; and it is upon adult material exclusively that we here report. It is possible that differences in pituitary size and intestinal length can not be demonstrated in immature birds, though the former was easily possible in Albino rats.

There are several sources of interest in these results. It is biologically—perhaps clinically—important that there is at present strong evidence that male and female are characterized by differentials in pituitary size (probably chiefly in anterior lobe) and intestinal length. The evidence points to the greater activity of the female pituitary as the cause of the longer female intestine. This same condition would also clarify the alleged earlier sexual maturity of the female. Again, such a relationship is important to an analysis of the hereditary basis of growth; length in a digestive apparatus may chiefly rest on a genetic factor related primarily to the degree of activity of the anterior lobe. Finally, in adults, it may become practicable to use the easily measured intestine as an index of the activity

*Obtained by Dr. Gertrude H. Transeau.

or size of the anterior lobe—the latter being a thing very difficult to measure in most laboratory animals.

SUMMARY

Adequate data from adult ring doves show that the females of these forms have longer intestines (5-10 per cent) than the males. The presence of *Ascaridia* is here associated with increased length of intestine in both sexes.

Some new data for pituitary size in pigeons of both sexes agree with earlier data (McCarrison) in indicating that in these animals the females have larger pituitary glands.

The few items of adequate data now available for man, rat and bird lead to the conclusion that there is a sex difference in both pituitary size and intestinal length, and that this difference involves a larger pituitary (particularly anterior lobe) and a longer intestine in the female. Some biological and clinical applications of these results are suggested.

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Abstract Department

Influence of the sodium salt of barbital on the effects of adrenin (Action de la diéthylmalonylurée sodique sur les effets vasculaires de l'adrenaline). Arnell, O., Compt. rend. Soc. de biol. **97**: 1633-1635. 1927.

When tested on a frog, sodium barbital in dilute solution, 25 parts in ten million, markedly reinforced the effects of dilute adrenin as shown by the slowing of the heart.—J. C. D.

Modification of adrenalin effect with functional status of stomach. Arquin, S. F. Proc. Soc. Exper. Biol. & Med. **25**: 97-99. 1927.

The work was done on normal trained dogs. Stomach balloons were passed by mouth, and records taken on a kymograph. After a suitable control period 10 minims of 1:1000 adrenalin was injected intracutaneously. It was found that the actively digesting stomach showed no reaction to adrenalin; the starving stomach in hunger contraction showed dilatation, with inhibition of contractions, in reaction to adrenalin; the starving stomach in the quiescent state was thrown into forcible hunger contractions. It is concluded that the tissue cells proper, or the myoneural filaments, by their tonus at the time of stimulation, are the determining factors as to the direction of reaction to adrenalin.—Author's Abst.

The fate of sugar in the animal body. VII. The carbohydrate metabolism of adrenalectomized rats and mice. Cori, C. F., and Gerty T. Cori, J. Biol. Chem. **74**: 473-493. 1927.

When rats surviving double adrenalectomy were subjected to a 24-hour fast, the liver glycogen disappeared and the blood sugar fell considerably below normal. In contrast to the liver glycogen, the glycogen content of the muscles of these animals remained the same as that of normal control rats fasted for the same length of time. The absence of liver glycogen in fasting adrenalectomized rats is not the result of a disturbance in the synthesis of sugar into glycogen, since liver glycogen is formed at a normal rate when glucose is fed. Adrenalectomized rats, fasting 24 hours, absorbed glucose at a much slower rate than 24-hour fasting normal rats. During 4 hours of glucose absorption the adrenalectomized rats without insulin oxidized 373 mgm. of glucose and formed 270 mgm. of glycogen (124 mgm. in the liver and 146 mgm. in the rest of the

body). The adrenalectomized rats receiving insulin injections oxidized 471 mgm. of glucose and deposited 37 mgm. of glycogen in the liver and 185 mgm. of glycogen in the rest of the body. The difference in liver glycogen of 87 mgm. corresponds closely to the difference in glucose oxidation of 98 mgm., while the glycogen deposition in the rest of the body (chiefly muscles) is slightly increased. The same results have been obtained previously on rats with intact adrenals, while a discharge of epinephrin in sufficient amounts to produce a metabolic effect could not be excluded. Since the adrenals were absent in the present experiments, the conclusion has been drawn that the lessened deposition of liver glycogen and the increased sugar oxidation, also to be observed in insulinized rats with intact adrenals, are due to insulin alone and not to a combined action of insulin plus epinephrin. Previous experiments have shown that insulin injections lead to a decrease in liver glycogen of fasting insulinized mice. An identical result has been obtained on mice from which both adrenals had been removed 20 to 30 days previously. The adrenalectomized mice without insulin showed 2.16 per cent liver glycogen after a fasting period of 1 to 5 hours. The adrenalectomized and insulinized mice that were killed simultaneously showed only 0.79 per cent liver glycogen. Since the effect of insulin on the liver glycogen of fasting animals is the same, whether or not the adrenals are present, there is no need to assume that epinephrin is responsible for the decrease in liver glycogen following insulin injections.—Author's Abst.

The depressor (vaso-dilator) action of adrenalin. Dale, H. H., and A. N. Richards, J. Physiol. **63**: 201-210. 1927.

An investigation was made of the alleged vasodilator effect due to liberation of histamine from the lung following small intravenous injections of adrenalin. The greater effect produced by intravenous injections as compared to intra-arterial injections reported by Burn and Dale (J. Physiol., **61**: 185. 1926) was found to be due to a technical error. The authors confirmed the conclusion that the vasodilator effect of adrenalin is due to peripheral action. However, it was observed that an injection of adrenalin into the arterial supply to the brain when the tone of the vasomotor center was raised by restricting the blood supply produced a very powerful depressor effect, apparently due to direct effects on the center.

—C. I. R.

Observations on hemodynamic effect of epinephrine in unanaesthetized dogs. Dragstedt, C. A., and A. H. Wightman, Proc. Soc. Exper. Biol. & Med. **25**: 22-24. 1927.

Observations following the continued intravenous administration of epinephrine in unanaesthetized dogs and dogs slightly narcotized with morphine are reported. Pressor effects were found to

occur with doses between 0.12 cc. and 0.5 cc. of 1 to 1 million adrenalin per kgm. per minute. Depressor responses were not seen. In animals in which depressor effects were seen during ether anaesthesia, only pressor effects were seen after recovery from the anaesthesia.—C. A. Dragstedt.

The vasomotor action of adrenin on muscle (Actions vasomotrices de l'adrénaline sur les muscles. Processus périphérique vasoconstricteur et processus central vaso-dilatateur.) Gayet, R., T. Gayet and M. Guillaumie, Compt. rend. Soc. de biol. **97**: 1145-1147. 1927.

The measurements were made on the paws of dogs anaesthetized with chloralose. Paw (I), Dog (A), was normal. Paw (II), Dog (A), was amputated and circulation maintained with Dog A by tubes. Paw (III), Dog (B), was amputated save for the sciatic and crural nerves and circulation derived from Dog A. Paw (IV), Dog (B), was normal. From their experiments with this arrangement, the authors conclude that the influence of adrenin on the circulation of muscle is, excluding the effects of changes in blood pressure in the general circulation, the result of two actions separate and opposed. Regardless of the dose there is constriction of peripheral origin and dilatation having its origin in the central nervous system. —J. C. D.

New researches on the heart-hormone (Neue Herzhormonbefunde). Haberlandt, L., Klin. Wchnschr. **44**: 2099. 1927.

The activity of solutions containing the heart stimulating hormone or the hormone in the heart itself are not destroyed by exposure to daylight, light from an incandescent lamp, ultra-violet light and Roentgen ray. Consequently this hormone differs from the cardiac accelerating substance of Loewi and adrenalin, which are destroyed by such treatment.—L. R. Dragstedt.

Glutathione and the reducing properties of tissues of decapsulated rats (Le glutathion et les propriétés réductrices des tissus des rats décapsulés). Houssay, B. A., and P. Mazzocco, Compt. rend. Soc. de biol. **97**: 417-419. 1927.

The striking result was the increased reducing power of muscle and kidney when tested with glutathione in the decapsulated animals. This reached a maximum at eight to fifteen days after operation and was normal after about thirty days. This reaction does not agree with the results when m-dinitro-benzene is used to test with, but is confirmed by the intensity with which the muscles stain in the nitroprussiate reaction.—J. C. D.

The vagus nerve and the secretion of adrenin from the adrenals (Nerfs pneumogastriques et secrétion surrénale d'adrénaline).

Houssay, B. A., and E. A. Molinelli, Compt. rend. Soc. de biol. **97**: 1343-1344. 1927.

Dog experiments in which the vagus was cut under local anaesthesia indicate that the vagus has no vasomotor effect either direct or reflex on the secretion of adrenin.—J. C. D.

The oral administration of epinephrine. Menninger, W. C., Arch. Int. Med. **40**: 701-714. 1927.

The author gives a rather complete review of the literature. He reports observations on 21 patients (16 of whom showed evidences of hyperthyroidism) following the oral administration of 2 to 6 mgm. of epinephrine in gelatin capsules on an empty stomach. A decrease in blood pressure of from 2 to 10 mm. was seen in 9 cases; no change in pressure in 6 cases; increase in pressure of from 5 to 15 mm. in 6 cases, and increase in pressure of 15 mm. or more in 7 cases. The rises in the latter seven were 16, 18, 20, 28, 30, 50, and 110 mm. Hg. The increased blood pressure lasted from 35 to 90 minutes. Abdominal cramps, substernal distress, respiratory distress, nausea, tremor, sweating and vomiting were also seen in some cases. The author concludes that the oral administration of epinephrin is inconstant and unreliable, but that in certain cases it is undoubtedly absorbed from the gastro-intestinal tract.

—C. A. Dragstedt.

The action of adrenin in asthma and hay fever (Le mécanisme de l'action de l'adrénaline dans l'asthme et le coryza spasmodique). Peruche, de Paula, Compt. rend. Soc. de biol. **97**: 1062-1064. 1927.

The author concludes that the efficiency of adrenin in asthma is due to its influence on CO_2. There is increased CO_2 in the blood in these conditions. Adrenin reduces the CO_2 tension in the blood, increases the CO_2 in exhaled air, reduces the CO_2 alveolar tension, but does not influence the pH of the blood.—J. C. D.

The hypertensive action of adrenalin following various routes of administration (L'action hypertensive de l'adrénaline suivant la voie d'introduction dans l'organisme). Plumier-Clermont and L. Garot, Arch. int. Physiol. **26**: 362-388. 1926.

Experiments are reported in which adrenalin was administered to dogs in various ways and the resultant effect on the blood pressure noted. No mention is made of the anaesthetic used. Subcutaneous injections of dilutions from 1-10,000 to 1-100,000 in doses of 1/60 to 1/3 mgm. per kgm. gave no clear-cut effects on the blood pressure, but quite regularly a slowing of the pulse. There was no relation between the effects observed and the size of the dose. Intramuscular injections of dilutions from 1-1,000 to 1-10,000 in doses of 1/10 to 1/3 mgm. per kgm. gave inconstant results, but there

was a greater tendency to pressor effects than on subcutaneous injections, which they attribute to better absorption. Slow intravenous injections of dilutions of 1-100,000 at a rate of 1 cc. per minute gave no appreciable effect. Larger doses gave pressor effects. No mention is made of any depressor effects. Administration via the gastrointestinal tract was made by laparotomy and injection of the adrenalin into the stomach or bowel by hypodermic needle. Doses of 1/20 to 1/2 mgm. per kgm. gave usually a fall in blood pressure of approximately 10 mm. Injection of adrenalin into the mesenteric vein was much less effective than by peripheral veins. This they attribute to a neutralization or storing in the liver and thus explain the ineffectiveness of gastrointestinal administration. Rectal administration they found more apt to be effective than gastric or intestinal, and attribute this to better absorption on the one hand and escaping the liver on the other. Intra-arterial injection was much less effective than intravenous, and there was a larger latent period. This they relate to the constitution of the arterial wall and the interposition of a capillary bed.—C. A. Dragstedt.

Does adrenin exert a stimulating action on the vaso-motor centers? (L'adrénaline exerce-t-elle une action stimulante sur les centres nerveux vaso-moteurs?). Tournade, A., Compt. rend. Soc. de biol. **97**: 1143-1144. 1927.

The kidney of a dog (A) was manipulated so that the blood supply was derived from a second dog (B), but the nerve supply from dog A remained intact. Intravenous adrenin injections into dog A resulted in the kidney dilating, contracting, or one condition following the other. There is an action of adrenin directly on the central nervous system causing vaso-constriction, but this is usually masked by the vaso-dilation, due also to action directly on the central nervous system.—J. C. D.

The effect of adrenalin on intestinal volume. White, A. C., J. Parmacol. Exper. Therap. **32**: 135-147. 1927.

In anaesthetized or decerebrated cats, after bilateral vagotomy, intravenous injection of adrenalin in doses varying from 0.0129 mgm. to 0.0323 mgm. per kilogram showed generally a diminution in intestinal volume. With doses varying from 0.0004 to 0.0732 mgm. per kilogram the predominant effect was an increase. In some cases there was a preliminary decrease followed by an increase in volume. Volume changes were independent of blood pressure.
—C. I. R.

Some recent advances in our knowledge of the ductless glands. Abel, J. H., Med. Clin. N. A. **11**: 113-126. 1927.

The physiological, chemical and pharmacological properties of the various endocrine glands are discussed. The problem as to

whether the posterior lobe of the pituitary body has one or three or more specific principles is discussed, and it is concluded that there is only one active principle. Inherent in this one principle are a surprising number of various physiological properties. Compared with histamine, heretofore the most powerful oxytocic or uterus-contracting agent known to medical science, the best and final posterior-lobe tartrates are found to be from 1,000 to 1,250 times more powerful. Corroborating support of various experimenters that there is only one posterior-lobe principle is quoted. The structure, functions, and chemical principles of the hypophysis cerebri are described to make evident what difficulties are encountered in the study of any one of the organs of internal secretion.—I. B.

Endocrine disorders as related to more common syndromes. Hutton, J. H., Med. Clin. N. A., **11**: 113-126. 1927.

This paper is a plea that more attention be given the endocrines by the profession at large in general physical examinations. An investigation of the condition of the ductless glands should be just as routine a procedure as the determination of the condition of the circulatory, gastrointestinal or genitourinary systems. Endocrine disorders are more prevalent than is generally supposed, and when discovered during their incipiency respond readily to appropriate treatment.—I. B.

Changes in water content of the liver as influenced by some of the internal secretions (Variations de la teneur en eau du foie après quelques modifications de l'equilibre endocrinien). The effect of insulin, thyroid extract, and adrenin on the water content of the liver. The thyroid-adrenal-pancreatic relationship (Action de l'insuline, de la thyroïde et de l'adrénaline sur la teneur en eau du foie. Correlations thyro-surréno-pancréatiques). Parhon, C. I., M. Cahane and V. Marza, Compt. rend. Soc. de biol. **97**: 1115-1118. 1927.

In sheep, thyroid extract increases the water content of the liver to a marked degree, adrenin less so, while insulin reduces it.

—J. C. D.

Influence of transplantation on the sex characters of earth-worms (Expériences de transplantation sur les caractères sexuels secondaires des lombriciens). Avel, M., Compt. rend. Soc. de biol. **97**: 1069-1070. 1927.

Transplantation after puberty does not influence the sexual cycle, but removal of the gonads before puberty prevents the development of the sexual cycle.—J. C. D.

Changes in the ovary of the mouse following exposure to x-rays. III. Irradiation of non-parous adult. Brambell, F. W. R., and A. S. Parkes, Proc. Roy. Soc. **101B**: 316-328. 1927.

Seventy-five per cent of adult animals killed five weeks or more after radiation were sterilized. The oestrous cycles of these animals were not interrupted. Oocytes of the small follicles were destroyed, leaving persistent "anovular" follicles. The cortical elements of the ovaries persisted and continued to produce oestrin without interruption after irradiation.—E. A.

Studies on distribution of the follicular hormone in the body (Recherches sur la distribution de la folliculine dans l'organisme). Brouha, L., and H. Simonnet, Compt. rend. Soc. de biol. **97**: 459-460. 1927.

The placenta of the cow and uterine muscle of the cow and mare were examined in addition to human blood from patients in various conditions. The authors conclude in part that in the organs examined the hormone, when found, was in weaker concentration than in the follicle. It, or a similar substance, exists in the blood during gestation. It is not present in the resting uterus. It is found in milk. In certain chronic amenorrheas it is found in the blood.—J. C. D.

Production of male characteristics in capons and senile cocks by injection of serum from young males. Activation by previous injection into the young males of serum from senile animals (Détermination ou retour des caractères de masculinité, chez les chapons et les viex coqs, par le sérum de jeunes animaux males. Activation du sérum par injection préalable au jeune male de sérum de vieil animal). Busquet, H., Compt. rend. Soc. de biol. **97**: 1463-1465. 1927.

The author concludes in part: Serum from young bulls, stallions, and rams cause the reappearance of male characters in capons and senile cocks. If a young bull is injected with serum from a senile bull, the serum from the young bull shows a marked increase in effects. The serum shows its full effects when given by mouth.
—J. C. D.

Gonad stimulating hormone of anterior pituitary and heterosexual ovarian grafts. Engle, E. T., Proc. Soc. Exper. Biol. & Med. **25**: 83-84. 1927.

Ovaries from 20-day old rats were transplanted into the abdominal muscles of adult castrated rats and into the testis of normal adults. Daily homeo-transplants of the anterior pituitary cause a high degree of follicular development in the ovario-testis. The ovarian graft in the testis does not differ histologically from that in the castrated male. The seminal epithelium of the host is normal in character. Although the elapsed time was short, there is no apparent "antagonism of the sex glands."—Author's Abst.

Pregnancy following superovulation in the mouse. Engle, E. T., Proc. Soc. Exper. Biol. & Med. **25**: 84-85. 1927.

Superovulation may be induced in the mouse and rat by daily transplants of the anterior pituitary, with from 20 to 48 ova in each uterine tube, as reported by Smith and Engle (Am. J. Anat., **40**).

Superovulation is followed by pregnancy in the mouse with from 19 to 29 foetuses recovered on the 9th or 10th day of pregnancy.—Author's Abst.

Clinical data obtained with the female sex hormone blood test. Frank, R. T., and M. A. Goldberger. J. Am. M. Ass. **90**: 106-110. 1928.

The ovarian hormone content of the blood of 86 subjects was investigated by mouse estrous assays. It was concluded that in women with normal sex cycle, more and more of the female sex hormone accumulates in the circulating blood until menstruation sets in. With the onset of menstruation, as well as with the beginning of pregnancy, the hormone disappears from the circulating blood. The hormone is found in great concentration in the menstrual as well as in the postpartum blood. The hormone is found in the circulating blood from the twelfth to the fortieth week of gestation. In functional bleeding a majority of cases show excessive ovarian activity. Functional overactivity may be demonstrated without excess bleeding ("tension"), and even in the presence of amenorrhea. Amenorrheas must be subdivided into (a) a grave type without cycle, and into those with (b) subthreshold cycle, (c) self-limited with impending menstruation, and (d) due to persistent corpus luteum. The gravity of the condition depends on the type. Women who have never menstruated may nevertheless ovulate and their sex tract undergo cyclic changes. Our test, when positive, permits of the determination of sex. Sterilities probably fall into two classes, the first with normal cycle, the second with depressed function. In the first group other factors besides ovarian function must be taken into account. Death of the fetus after the twelfth week can be recognized by the blood test.—R. G. H.

Further experiments on hermaphroditism in the presence of an intact testis (Nouvelles expériences sur l'hermaphrodisme expérimental en présence de testicules intacts.) Lipschütz, A., Compt. rend. Soc. de biol. **97**: 1401-1402. 1927.

Ovarian transplants into male guinea pigs, each with one testis intact, produce evidences of feminization in from five to nine weeks when tried in Chile. In North Europe these same results take five to eight months to develop.—J. C. D.

Impregnation by a guinea pig rendered hermaphroditic (Fécondation par le cobaye expérimentalement hermaphrodite). Lipschütz, A., and E. Vinals, Compt. rend. Soc. de biol. **97**: 1400-1401. 1927.

Two males with intact testes were feminized by ovarian transplants. The mammary glands were actively secreting. At this time they impregnated three normal females.—J. C. D.

On the occurrence of the oestrous cycle after x-ray sterilization. Part III. The periodicity of oestrous after sterilization of the adult. Parkes, A. S., Proc. Roy. Soc. B, **101**: 421-449. 1927.

The length of pretreatment (control) cycles is compared with the length of cycles after x-ray sterilization in more than 60 animals The periodicity of oestrous was not significantly affected by x-ray elimination of the follicles and corpora lutea. The variability of the post-irradiation cycle was greater than that of the pre-irradiation cycle.—E. A.

Ovum and hormones. Zondek, B., and S. Aschheim, Klin. Wchnschr. **6**: 1321-1322. 1927.

The paper deals with several questions, fundamental to gynecology on the basis of a large series of well considered experiments carried out on the mouse. 1. What happens when the ovum is destroyed? In corroboration of the work of Parkes, it is found that radiation of the ovaries in sufficient dosage to destroy every vestige of ova and follicles does not prevent the recurrence of oestrous cycles, a result that seems to support Steinach's theory of the function of the interstitial tissue. 2. Does ovarian hormone cause ripening of the ovum? Injection of folliculin into infantile females causes oestrus changes in uterus and vagina, but no immediate ripening of ova. 3. Finally, what happens if hormone production is inhibited? Females fed thorium have ripe Graafian follicles, but show no oestrus and no changes in the genital tract; but if anterior hypophyseal extract is injected along with the thorium the animal goes into heat. Hence the anterior lobe hormone is the "motor" that sets the oestrous mechanism going by acting through a responsive ovary. Ovum and ovarian hormone are, therefore, coördinated, but not causally related, and both are under the control of the pituitary.
—Carl Hartman.

The so-called pars intermedia of the human hypophysis (Über die sogenannte Pars intermedia der menschlichen Hypophyse). Dayton, T. R., Ztschr. f. Anat. u. Entwcklngsgesch. **81**: 359-370. 1926.

From an examination of over 100 normal adult human hypophyses and some from infants, the author concludes that in the human adult there is no true pars intermedia. Either the anlage of pars intermedia of the embryo disappears entirely or, what is more probable, has become something quite different, namely, mucous glands, which can be seen in children, but not in adults, or small basophilic cells. The stratified epithelium between the lumen

of Rathke's pouch and posterior lobe during later development becous glands, which can be seen in children but not in adults, or the growth of the pouch or stops growing entirely. From the fact that the cells about the colloid vesicles may be exactly the same in structure as those of the anterior lobe, and in pregnancy, castration, and certain pathological changes in the reproductive glands (a case of his own is described) may show the same changes as occur in the anterior lobe cells proper, the author thinks that all of the colloid vesicles are derived from the anterior lobe. Occasionally there are small areas where the epithelium of the vesicles is ciliated.—A. T. R.

Note on the mechanism of pituitary hyperglycemia (Sur le méchanisme de l'hyperglycémie hypophysaire). Nitzescu, I. I., and P. Ramneantu, Compt. rend. Soc. de biol. **97**: 1105-1106. 1927.

If the blood sugar level of the arterial blood entering a muscle is compared with that of venous blood leaving it, the level in the venous blood is lower normally, but higher following injections of posterior lobe extract.—J. C. D.

The peduncle of the human hypophysis (Sul peduncolo dell'ipofisi umana). Orlandi, N., Rev. sud-am. de endocrinol. **10**: 839-896. 1927.

An extensive anatomico-pathological study of the peduncle of the hypophysis is given, including tuber cinereum, infundibulum, pars nervosa and pars linquiforme (pars tuberalis). The following are among the important conclusions. The pars nervosa of the peduncle contains nerve fibers which arise from nuclei in the tuber cinereum and go to end in the neurohypophysis. During their course they give fibrils to vessel walls and to the epithelium of the pars linguiforme (tuberalis). The supporting tissue of the peduncle is represented by microglia and the rare elements of fibrous neuroglia. The capillaries of the peduncle are typically sinusoidal. They have a characteristic precollagenous reticular tissue adventitia, but no membrane of Held. The "gitterfasern" is found in the pars linguiforme and merely surrounds the vessels in the pars nervosa. Different types of pigment cells are described. In pregnancy the peduncle does not show any changes of note other than a predominance of cells with dark nuclei in the pars linguiforme during the latter months of gestation. In cases of chronic nephritis the vessels of the peduncle contain a homogeneous lipoid substance arising from the prehypophysis, probably in conjunction with the increase of basophil elements. Inflammatory processes of the meninges, either acute or chronic, seldom affect the peduncle. In some cases of diabetes mellitus and in polysarcia there is an infiltration of lymphocytes in the peduncle and the tuber cinereum. Cysts have been observed which have arisen from degeneration in the center of nodes of pavement epithelium and from dilatation of the tubules of the

pars linguiforme. The hypophysis is frequently the site of neoplastic metastases. In conclusion, the author expresses the conviction that the several parts of the peduncle and the hypophysis constitute a system and that histopathological researches in this region must be considered incomplete if they fail to take cognizance of all the parts of this system.—W. J. A.

Oxytocic power of pituitary under different circumstances (Der Gehalt des Hypophysenhinterlappens an uteruserregender Substanz unter verschiedenen Bedingungen). Pak, C., Arch. f. exper. Path. u. Pharmakol. **114**: 354-361. 1926.

After removal of the ovaries in rats the uterus was less inclined to spontaneous contraction, but the potency of the pituitary extract in oxytocic principle was not decreased. Thyroidectomy, arsenic poisoning, CO-poisoning, and intensive Röntgen irradiation were all ineffective. After $HgCl_2$ and diphtheria toxin poisoning and to some extent after thyroid feeding, the oxytocic potency of extracts was decreased. Faradization of the cervical sympathetic produced an increase in four out of five instances.—C. I. R.

Report of a case of diabetes insipidus. Peabody, F. W., Tr. A. Am. Physicians, **40**: 170-176. 1925.

The case reported occurred in a white woman, 61 years old. The diagnosis of diabetes insipidus in this case was based upon the sudden appearance of great thirst, polyuria, and the excretion of a urine with a specific gravity which, although not quite so low as that commonly seen in this condition, approximated it; on the evidence of the inability of the kidney to concentrate the urine, as shown by the 2-hour test; and on the decrease of urinary output with increase of the specific gravity of the urine following the injection of pituitrin. The disease lasted four years and was characterized by alternating cycles of several months' duration. There was, however, a gradual tendency to improvement, so that while she was almost confined to the house during the first year, she was able to travel in the last year. Having passed through the series of remissions and relapses, she seemed to have reached a state of comparative relief from diabetes insipidus at the time when she developed another and fatal condition apparently unrelated to it. The most interesting clinical problem involved was that of the etiology. The usual causes of the symptom-complex of diabetes insipidus—tumor, syphilis, tuberculosis, fracture of the skull, or cerebral hemorrhage in the ordinary sense—could apparently be excluded, and, while no definite proof could be offered, the almost simultaneous onset of the diabetes insipidus and the hemorrhagic tendency led the majority of the many physicians who considered the case to regard the diabetes insipidus as the result of a small hemorrhage which happened to take place in the substance of the hypophysis. The occurrence of the bleeding

into the vitreous of the eye shows that in the hemorrhagic condition from which she suffered the bleeding was not limited to the subcutaneous tissues, and the pathological condition of the hypophysis as revealed at autopsy might well be explained on the basis of hemorrhage. The fact that no similar case has been reported in the literature gives to this instance a special significance.—I. B.

Glycemia, glycogen. and the action of insulin in decapsulated rats (La glycémia, le glycogène et l'action de l'insuline chez les rats décapsulés). Artundo, A., Compt. rend. Soc. de biol. **97**: 411-413. 1927.

The glycemia falls slightly three to eight days after removal of the adrenals, rises somewhat above normal at two weeks, and becomes normal at five weeks. The liver glycogen is decreased up to eight days, increased at two weeks, and normal at five weeks. The muscle glycogen is increased at three days, reduced at fourteen days, and normal at five weeks. The operated animals were very susceptible to insulin at two weeks, and less so at five weeks, though more so than the controls. In them the insulin reduced the liver glycogen regularly and the muscle glycogen less regularly.—J. C. D.

Acetates in normal and diabetic blood (Les Acetates dans le sang normal et diobetique). Bruno, A., Compt. rend. Soc. de biol. **97**: 1512. 1927.

In normal dogs there are 1 to 1.5 mgm. of acetic acid per 100 cc. of blood. This is increased in diabetes and reduced under insulin.—J. C. D.

The fate of sugar in the animal body. IV. The tolerance of normal and insulinized rats for intravenously injected glucose and fructose. V. A seasonal occurrence of ketonuria in fasting rats accompanied by changes in carbohydrate metabolism. Cori, C. F., and Gerty T. Cori, J. Biol. Chem. **72**: 597-625. 1927.

The intravenous glucose tolerance of non-fasting male rats is at a rate of infusion of 2.5 gram per kgm. of body weight per hour. An identical value has been obtained on rats fasted previously for 48 hours. The intravenous tolerance limit of mice is close to 2.5 grams of glucose per kgm. per hour. The absorption of glucose from the intestine of the mouse proceeds at a rate of 4.6 grams per kgm. per hour and leads to glycosuria. In the rat, the rate of absorption of glucose from the intestine is lower than the intravenous tolerance rate. The tolerance of fasting rats for fructose, when infused into the femoral vein, is at a rate of 0.35 gram per kgm. per hour. However, for an infusion into a mesenteric vein, the tolerance limit is at a rate of 0.7 gram per kgm. per hour. In non-fasting rats, the tolerance limit is at a rate of 0.65 gram of fructose per kgm. per hour. When glucose or fructose is infused above the

tolerance rate (4.5 grams per kgm. of rat), there is no marked difference in the rate of utilization of these two sugars. Large doses of insulin raise the intravenous glucose tolerance from 2.5 to 3.0 grams per kgm. per hour, or by 20 per cent. Normal rabbits show an intravenous tolerance rate of 0.9 gram of glucose per kgm. per hour. After insulin treatment the tolerance increases to 1.3 grams per kgm. per hour or by 40 per cent. Insulin is without effect on the tolerance for intravenously injected fructose.

Rats, during the summer months, excrete from the 24th to the 48th hour of fasting an average of 6.2 mgm. of total acetone bodies per 100 grams of body weight per 24 hours. During the winter months the excretion of acetone bodies was only 1.9 mgm. per 100 grams per 24 hours. When rats were kept for 3 weeks in winter at a room temperature comparable to that of the summer, the excretion of acetone bodies did not rise, showing that the summer heat is not directly responsible for the occurrence of ketosis in fasting rats. The intravenous glucose tolerance of rats suffering from summer ketosis was at a rate of 1.6 grams per kgm. per hour. This is 36 per cent lower than the values obtained in winter on rats without ketosis (see the preceding abstract). The lower glucose tolerance was due to a lessened ability of the tissues to oxidize glucose, while the glycogen storage in the tissues was not changed. From 721 grams of glucose that were absorbed in 4 hours by the rats in summer, 131 mgm. were oxidized, while 380 mgm. were converted into glycogen. In winter, for an almost equal glucose absorption, the oxidation and glycogen formation amounted to 281 and 388 mgm., respectively. Insulin injected into rats suffering from summer ketosis increased the amount of glucose oxidized. It is concluded that ketosis is associated with a reduced functional activity of the pancreas and, in consequence of this, with a reduced capacity of the tissues to oxidize glucose.—C. F. Cori.

The management of diabetes mellitus associated with pulmonary tuberculosis. Elliott, C. A., and W. H. Nadler, Med. Clin. N. A. **9**: 1453-1472. 1926.

Because of the conflicting indications in the dietary treatment of diabetes and phthisis, the combination of the two diseases was formerly regarded as fatal. The use of insulin has made it possible to meet the requirements of both conditions, and as a result of the better management of diabetes. The prognosis of cases complicated with tuberculosis has been greatly improved. Four case histories illustrate this point. Normal glycemia favors the healing of tuberculous lesions; hyperglycemia predisposes to their extension.—I. B.

Glycemia as a practical guide in the treatment of diabetes mellitus. Elliott, C. A., P. Starr, and W. H. Nadler, Tr. A. Am. Physicians, **40**: 316-320. 1925.

The occurrence of frequent fluctuations in the general level of blood sugar in diabetes mellitus is emphasized. The maintenance of normal glycemia is emphasized as essential to efficient diabetic treatment. A procedure making possible the continual supervision of the blood-sugar level in patients with diabetes is described and illustrated.—I. B.

Clinical problems in the management of diabetes with a review of four fatal cases. Fitz, R., Med. Clin. N. A. **10**: 1163-1174. 1927.

In order to discuss a few phases of the problem of diabetes, the author describes in detail two cases of diabetes with tuberculosis, one with duodenal ulcer and one with marked tonsillar infection. Tuberculosis as a complication of diabetes is frequent and often overlooked. X-ray examinations of the chest in diabetic patients are advocated. All discoverable foci of infection should be given prompt attention. A careful physical examination of each case of diabetes should be made at least twice a year, as normality of weight, general appearance and blood and sugar determinations do not necessarily exclude serious complications. Education of patients on the diabetic question is vital. Finally, the physician undertaking the care of a diabetic patient must be properly equipped in the management not only of the physical, but also of the mental aspects of the individual.
—I. B.

Demonstration by pancreatic transplantation of the control of the internal secretion of the pancreas through hormones. Experiments on normal animals (La régulation de la sécrétion interne pancréatique par un processes humoral, démontrée par des transplantations de pancréas. Expériences sur des animaux normaux). Gayet, R., and M. Guillaumie, Compt. rend. Soc. de biol. **97**: 1927. 1613-1614. 1927. **Experiments on depancreatized animals (Expériences sur des animaux dépancréatés.)** Ibid. 1615-1618.

Experiments on one normal and three depancreatized dogs are reported. The pancreas from a donor was transplanted into the carotid jugular circulation of a recipient. The blood sugar was followed over a period up to two days. In normal dogs the transplant did not influence the blood sugar. In depancreatized dogs, which were markedly hyperglycemiac, introduction of the transplant was followed by a steady fall of blood sugar to a normal level. When the transplant was removed, the blood sugar rose again to a pathological level.—J. C. D.

An unusual case of diabetes mellitus: death after thirteen years' observation; necropsy. Gordon, A. H., C. L. Connor and I. M. Rabinowitch, Am. J. M. Sc. **175**: 22-31. 1928.

A case of diabetes mellitus is reported. The patient was under observation for thirteen years, during which time complete records

of clinical and metabolism findings were kept. This case demonstrates that, in spite of a very clear history, it does not necessarily follow that diabetes following repeated attacks of gall-bladder disease is due to the latter. This may explain the failures at times of surgery to alleviate or improve diabetes when associated with disease of the biliary passages. This case also emphasizes the fact that the clinical picture (the attitude, expression, color, nutrition, etc.) is not a reliable index of progress of insulin-treated diabetics. Blood analyses are here indispensable. This patient appeared to be well nourished and felt well. The post mortem findings, however, showed that the skin did not contain fat, but water. Also because of the long duration of the disease and the arteriosclerosis, other evidence of active diabetes (glycosuria) was masked. The patient had a raised renal threshold for sugar. This case is also another demonstration of the relationship between the cholesterol content of the blood and prognosis. The differential diagnosis during the final stages of the disease was difficult, because of a combination of findings not uncommon, but not frequently mentioned in the literature. Cerebral manifestations of diabetic coma may simulate those of uremia or cerebral hemorrhage. Suppression of urine, albumin and casts, high blood urea and creatinin, leukocytosis altered reflexes and fever were all present in this case. Other clinical features of interest were the presence of insulin edema, the color of the skin and the absence of response to insulin. The pancreas and the blood vessels of the brain were the organs of special interest in post mortem.—Author's Abst.

Results of prolonged treatment of normal animals with insulin (Récherches expérimentales sur le traitement prolongé des animaux normaux par l'insuline). Hornung, S., Compt. rend. Soc. de biol. **97**: 1500-1502. 1927.

Dogs show a decreasing influence of insulin on the blood sugar.
—J. C. D.

Adiposity and other etiological factors in diabetes mellitus. Anders, J. M., and H. L. Jameson, Tr. A. Am. Physicians, **40**: 230-245. 1925.

From statistical studies it appears that the death-rate from diabetes in Philadelphia had been increasing steadily until checked by the use of insulin about the middle of 1923, and that the incidence in patients under the authors' personal observation has been increasing steadily up to the end of 1924. Whereas in 1913, the numerical rating of diabetes as a cause of death assigned it to 22nd place, 10 years later it occupied 12th place, corresponding with what was found in the Registration Area of the United States and in New York in 1920. After the age of 40, women showed a decidedly higher diabetes death-rate and heavier incidence than men during

the past two decades, while for the like preceding period, the preponderance of deaths from this complaint occurred in males. This change in the influence of the sexes upon the mortality rate is inexplicable. In the authors' series of 1306 cases of adiposity, which includes 119 cases of diabetes, this sex relationship was also noted with respect to the incidence of the disease. The excess of deaths among females has progressively increased in Philadelphia in recent years until the sex ratio reached approximately 2 to 1 in favor of females. The predominant effect of adiposity as a predisposing cause of diabetes is clearly indicated by interesting tables. Only 1 in 12 obese subjects develop diabetes among Gentiles, and 1 out of every 8 among Jews. Whether the higher ratio among the Jewish race is owing to greater susceptibility to the disease or a relatively great degree of overweight alone, as Joslin believes, is perhaps an unsettled question. The phenomenal rise in the diabetes death-rate and incidence among women in recent years is not due solely to their greater and more general adiposity. The cases of diabetes have multiplied themselves five times since 1880; but it cannot be justly claimed that overweight has increased in degree to a like extent. Finally, in 18 per cent of this series the disease occurred in persons of normal or even subnormal weight.—I. B.

Diabetic coma and its treatment. Joslin, H. F., and Priscilla White, Med. Clin. N. A. **10**: 1281-1305. 1927.

Coma and cancer caused 6 deaths among the 1,138 diabetic patients seen by the authors during the year ending July 1st, 1926. Forty-five of the living group of 200 or more children have already had coma 53 times; in 9, diabetes was discovered during coma. Coma is today as dangerous as ever, but far less fatal; but 10 per cent of the authors' fatalities last year were due to coma. Coma is preventable. The danger of the alkali treatment of diabetic coma is now supported by clinical evidence in the possibility of occurrence of alkalosis following recovery from coma in patients to whom no alkalies were given. We must differentiate between diabetic coma, coma due to hypoglycemia, and coma caused by renal block with retention of non-protein nitrogen, as well as other conditions associated with coma.—I. B.

Insulin, blood pressure, and vagus tonus (Insuline, tension artérielle et vagotomie). Jung, L., and L. Auger, Compt. rend. Soc. de biol. **97**: 1163-1164. 1927.

There was a decrease in the response of the heart to vagus stimulation when tested by the eye heart reflex, as the blood pressure fell following insulin injection in dogs.—J. C. D.

Glucose as a physiological excitant of the internal secretion of the pancreas (Le glucose excitant physiologique de la sécrétion interne

du pancréas). Képinov. L., and Petit-Dutaillis, Compt. rend. Soc. de biol. **97:** 1597-1598. 1927.

Deprancreatized dogs were kept in carbohydrate equilibrium by small pancreatic grafts. Injections of glucose resulted in a protracted elevation of the blood sugar level instead of an elevation followed by reduction below normal, found in animals with the pancreas intact.—J. C. D.

Does the nervous system influence the supply of insulin under normal conditions? (Le système nerveux intervient-il dans la régulation de l'insulinémie physiologique?). LaBarre, J., Compt. rend. Soc. de biol. **97:** 1184-1187. 1927.

Vascular anastomosis between two dogs was established. The vagi of the donor were cut. The pancreas of the recipient had been removed. The hyperglycemia of the recipient was not modified. Similar results followed when the donor's pancreas was entirely isolated. If the nerve supply to the donor's pancreas was left intact, the blood sugar of the recipient is reduced. The secretion of insulin is therefore dependent on the vagus nerve.—J. C. D.

Increased insulin output following injection of posterior hypophysis extract (Hyperinsulinémie consécutive a l'injection d'extrait hypophysaire postérieur). La Barre, J., Compt. rend. Soc. de biol. **97:** 1416-1419. 1927.

The experiments were tried on dogs deprived of their adrenals. —J. C. D.

A relationship between body temperature and blood sugar in rabbits. Lawrence, R. D., J. Physiol. **63:** 12-13. 1927.

An account of an observation that in rabbits a spontaneous rise in blood sugar was accompanied by a lowering of body temperature by as much as 5° F. in some cases. This phenomenon was observed in only seven out of 100 rabbits and usually occurred when animals were excited. The author suggests that this is an adrenalin reaction produced sometimes by excitement, sometimes as a reaction to the fall in blood sugar produced by insulin and sometimes as a reaction to collapse of undetermined origin. This suggestion is supported by the fact that the hyperglycemia occurring in rabbits when temperature is lowered is prevented by bilateral splanchnectomy and by the fact that ergotamine will prevent the increase. As a precaution the author suggests more than one preliminary test in determining the influence of a substance on blood sugar of rabbits.—C. I. R.

The state of blood sugar and adrenalin skin reactions after quartz-mercury vapor lamp irradiation and after sun baths (Das Ver-

Schweiz. med. Wchnschr. **57**: 759-761. 1927.

halten des Blutzuckers und der Adrenalinquaddel nach Quartzlampenbestrahlung und nach Sonnenbädern). Messerle, N.,

An investigation of the effects of two kinds of irradiation on blood sugar, alimentary hyperglucemia and on the reactions of the sympathetic nervous system. Twenty human subjects were used. After fasting over night, 20 grams of glucose were ingested and the glucemia curve determined during 90 minutes, after which subjects received 30-minute sun baths or 16-20-minute mercury vapor lamp irradiations at 60-80 cm. After 16-20 hours the glucemia curve was again determined. Fasting glucemia was diminished 16-20% and the glucemia curve leveled off after both kinds of irradiation, but the latter was more effective. In case of 4 subjects markedly pigmented from previous phototherapy, this treatment produced no such effects until the duration of irradiation was increased. In an attempt to determine the effect of irradiation on the sympathetic nervous system, intracutaneous injections were given of 0.1 cc. of 1:1,000,000 adrenalin, 30 minutes, 3 hours and 20 hours after irradiation. Wheals appeared in 5 minutes and reached their greatest diameter in 15 minutes and persisted to 30 minutes, after which there was recession. There was no noticeable difference in the reaction after each kind of irradiation. As compared to controls, the reaction was always more pronounced following irradiation, even as long as 20 hours after. These results, the author interprets as indicating that irradiation decreases tonus and irritability of the sympathetic nervous system.—C. I. R.

✓ **Pregnancy and diabetes.** Parsons, Eloise, L. W. Randall and R. M. Wilder, Med. Clin. N. A. **10**: 679-688. 1926.

Diabetic women usually do not become pregnant. Gonadal atrophy in diabetics of both sexes with associated functional deficiency is common. The danger of pregnancy to diabetic women is grave and has been regarded as an indication for therapeutic abortion. It is doubtful whether patients with severe diabetes ever survived pregnancy in the pre-insulin era. The authors report in detail their series of 11 cases of pregnancy in diabetic women; one with very mild diabetes of 17 years' duration had three pregnancies and three children; the pregnancies of the other ten women resulted in five children, two still births, and four miscarriages. In two of the patients suffering with moderately severe diabetes pregnancy was successfully completed. These young women had been treated previously for severe acidosis and depended largely on insulin when they later became pregnant.—I. B.

Insulin-thyroid antagonism. Rosenberg, M., Klin. Wchnschr. **6**: 631. 1927.

The author studied the effect of insulin on glycosurias in pure hyperthyroid cases and glycosurias due to thyroid administration, and those produced by thyroid administration to diabetics. In non-diabetics he finds that insulin does not appreciably lower the sugar output; in diabetics, glycosuria is induced by thyroid extract, and this promptly responds to insulin. The author thinks that in diabetics the insulin and thyreoidin are directly antagonistic and that the thyreoidin affects the carbohydrate metabolism in a diabetic directly by a synchronous hypofunction of the islands, and that this action is different than that in a non-diabetic. In a case of mild diabetes and one of glycosuria innocens, very large doses of insulin had to be used in order to diminish the glycosuria.—H. J. J.

Ocular disturbances in diabetes. Ruedemann, A. D., Ann. Int. Med. **1**: 39-43. 1927.

A clinical discussion of the ocular disturbances in diabetes. (No bibliography.) The author emphasizes the importance of examining the blood for the loss of vision of unknown origin. Hyperopia and myopia also may be present. Weakness or paralysis of the muscles supplied by the third nerve are most frequently encountered. Retinitis and iritis are also frequently associated with diabetes.—E. L.

Diabetes and pregnancy. Strouse, S. and P. A. Daly, Med. Clin. N. A. **9**: 1491-1497. 1926.

Though sugar is frequently found in the urine of pregnant women, diabetes mellitus as a complication of pregnancy is comparatively infrequent. Four cases of diabetes complicating pregnancy are detailed. Individualization in the treatment of these patients is vital. Pregnancy may upset the metabolic balance in an otherwise normal woman to the extent of producing a temporary clinical picture of diabetes, and may require mere dietary adjustment to tide her through pregnancy to normality. If, however, an already severely diabetic woman becomes pregnant, insulin treatment may be necessary to enable her to take the required calories under existing needs.—I. B.

Insulin and the treatment of juvenile diabetes mellitus. Toverud, K. U., Norsk Mag. f. Laegevidensk. **88**: 956-1010. 1927.

The author studied forty-seven children with diabetes mellitus. Most of these were patients at the Riks Hospital and some of them were under observation as long as four years. Only 17 per cent of the children had diabetes in their family; but diabetes followed acute infections in 26 per cent. The diet was based on the patient's carbohydrate tolerance. Three grams of protein was given for each kilo of body weight in children under seven years of age, and 2

gms. per kilo in the older ones. When the keto-antiketonic ratio exceeded 1.75 —1, symptoms of acidosis usually developed. It is concluded that diabetic children should have three daily injections of insulin, in order to keep their blood sugar approximately normal. When severe diabetes was present, or when the disease was chronic, it was possible to keep the blood sugar level normal during the day, but the level rose steadily during the night. The children developed normally, both physically and mentally. The carbohydrate tolerance remained stationary and even increased in seven children. These were very faithful to their diet and suffered from relatively few acute infections. In the other cases the tolerance decreased, either because of laxity in the diet or because of severe frequent infections, or both. The mortality was 36 per cent. Five of the children died in coma brought about by acute infections. One died after a fracture of the hip. In four cases the parents refused the insulin treatment, and in the other seven the diet was broken continually and the administration of the insulin was very irregular.—Daniel J. Glomset.

Permeability of the peripheral tissues for dextrose in epinephrin diabetes (Ueber die Glukosepermeabilität der peripheren Gewebe beim Adrenalindiabetes). Wiechmann, E., Deutsches. Arch. f. klin. Med. **154**: 296-304. 1927.

The author has shown experimentally that the sugar content of arterial and venous plasma runs parallel, being in a fasting individual somewhat lower in the venous plasma. Forty to fifty minutes after an intake of 100 grams of glucose by mouth this difference is increased; 60 minutes after injection of 1-2 mgm. adrenalin, in spite of a marked hyperglycemia, this difference between arterial and venous blood is nearly the same as in fasting blood. In the first case the difference is 4 times as large as in fasting blood, whereas after adrenalin it is but 1.2 times as great. The same figures apply to whole blood sugar determinations. The author thinks that the sugar exchange between plasma and erythrocytes does not explain the finding, but that the permeability of the tissues for glucose is lowered through adrenalin; in this sense the adrenalin diabetes is identical with clinical diabetes, for in both the glucose-permeability of the peripheral tissues is lowered.

—H. J. J.

Hyperthyroidism, myxedema and diabetes. Wilder, P. M., Tr. A. Am. Physicians, **41**: 113-146. 1926.

In a study of a series of 38 cases of diabetes mellitus combined with varying degrees of hyperthyroidism and in one case with myxedema, the author concludes as follows: The association of diabetes with hyperthyroidism occurs in about 1.1 per cent of all

cases of hyperthyroidism. Exophthalmic goiter is less frequently complicated by diabetes than adenomatous goiter with hyperthyroidism. Alimentary glycosuria is far more frequent, but is not included in these observations. Symptoms of hyperthyroidism may be obscured by those of diabetes, especially in severe acidosis or diabetic coma. One must be on guard for hyperthyroidism in all cases of diabetic acidosis. A mild diabetes may become severe by hyperthyroidism, and hyperthyroidism in crisis may provoke coma in a diabetic patient. The requirement of insulin is increased by hyperthyroidism. Iodin therapy in subjects of both exophthalmic goiter and diabetes reduces the intensity of the latter, but this drug does not influence the diabetes in patients with toxic adenoma. Iodin has no effect in uncomplicated diabetes. Thyroidectomy is usually followed by improvement in diabetes complicating hyperthyroidism. Operation in these patients is, however, more hazardous. It seems that at lower metabolic rates the tissue cell is capable of utilizing a given quantity of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased.—I. B.

Studies in calcium and carbohydrate metabolism. I. Calcium and glucose tolerance in diabetes mellitus. Wishnofsky, M., J. Lab. & Clin. Med. **13:** 133-138. 1927.

A review is given of the relationship between calcium and carbohydrate metabolism. There occur simultaneously changes in calcium and carbohydrate metabolism in diseases of the adrenals, thyroid, parathyroids, and pituitary glands. This is also true in various miscellaneous pathologic states such as: pregnancy, changes in H-ion concentration of the blood, diureten and phloridzin glycosuria, pneumonia, tuberculosis, and other infectious diseases. Many observers have found a negative calcium balance in diabetes mellitus. Both Von Moraczewski and Kahn observed that the administration of calcium ameliorates the diabetic state. Employing the glucose tolerance test as an index of the severity of diabetes, the author concludes that calcium in no way improves the ability of the diabetic to metabolize glucose.—Author's Abst.

Cause of hyperinsulinemia in the pancreatic vein following dextrose hyperglycemia (Sur les cause de l'augmentation de la teneur en insuline du sang veineux pancréatique lors de l'hyperglycémie provoqueé par injection de dextrose). Zung, E. and J. LaBarre, Compt. rend. Soc. de biol. **96:** 708-710. 1927.

Dogs were used. The pancreatic vein of a donor was connected with the jugular vein of a recipient who had previously been adrenalectomized. The blood sugar level was followed in the recipient and regarded as a measure of the insulin received by way

of the pancreatic vein of the donor. With both vagi intact, injection of sugar into the blood of the donor produces insulin in the pancreatic vein. Less insulin is produced if the right vagus is cut. If both vagi are cut or paralyzed with atropin, insulin does not appear.—J. C. D.

Topography of the parathyroids in swine (Zur vergleichenden Anatomie der branchiogenen Organs II. Zur Topographie der Epithelkörperchen beim Schwein, mit besonderer Berücksichtigung der Eignung des Schweins für die Gewinnung organotherapeutischer Epithelkörperchenpräparate). Arndt, H. J., Ztschr. f. Anat. u. Entwcklngsgesch. **81**: 191-197. 1926.

No parathyroids could be found in swine by macroscopic means. Many small masses in the neighborhood of the thyroid proved to be either accessory thyroids or lymph nodes. Microscopical examination of serial sections of the entire cervical region of fetal pigs and one pig a few days old revealed regularly one pair of parathyroids in the anterior horns of the thymus near the salivary gland. Adult pigs were not examined microscopically. The thymus extends unusually high into the cervical region in the pig. In the case of one young suckling pig the parathyroid gland on one side was not entirely surrounded by thymus tissue. In no case were the parathyroids in or near the thyroid. Apparently it is almost a hopeless task to get pure parathyroid extract from swine material. On the other hand, the pig thyroid is suitable as a source of parathyroid-free thyroid extract. No oxyphile cells nor colloid were seen in the parathyroids.—A. T. R.

Metabolic effect and clinical application of Collip's parathyroid hormone (Stoffwechselwirkung und klinische Verwendbarkeit des Epithelkorperschenhormons [Collip]). Brehme, T. and P. Gyorgy, Jahrb. f. Kinderh. **118**: 143-178. 1927.

An exhaustive study was made of the blood, urine, and stools in normal and tetanic children. The administration of Collip's hormone in non-tetanic as well as in tetanic children is followed by an increase in calcium, a slight lowering of the Phosphorus content and a shifting of the blood reaction to the acid side, with, however, an unchanged alkali reserve. The characteristic findings in the urine during the administration showed in normal infants an increase in titratable acidity with an increase in the calcium and phosphorus excretion. The values of the organic acids and nitrogenous elements were increased. The total calcium and phosphorus were not increased in two cases of puerile tetany after the administration. The effect of parathyroid extract is not constant as in some cases of tetany the results did not coincide with others. One case of tetany which could not be benefited by intensive antirachitic

treatment was improved by parathyroid extract. The authors conclude that the ordinary tetany of infancy is not of parathyroid genetic nature and the administration of this extract is not in the form of substitution therapy. The inconstant effect of the extract in addition to the occasional appearance of coincidental hypercalcemia symptoms (pallor, vomiting, abnormal stools, apathy, drowsiness, disturbed circulation, nephritic disturbances and sometimes death) speaks against the general application of the parathyroid hormone.—M. B. G.

Parathyroid extract in infantile tetany, report of a case. Gibson, A. H., Am. J. Dis. Child. **34**: 835-841. 1927.

Four cases of infantile tetany were treated with parathyroid extract (Collip), the dosage being that recommended by Hoag and Rivkin—5 units per kilogram of body weight for each milligram of rise in serum calcium desired. The total dose was administered in equal fractions hypodermatically at 4 to 6 hour intervals over a period of 24 to 36 hours. In 3 cases the rise in calcium and phosphorus was definitely related to the recovery from infection as evidenced by the drop in temperature and apparently not related to the treatment with the extract. In one case the temperature remained high and the serum calcium and phosphorus values failed to rise on administration of parathyroid extract. This case was complicated by thymic enlargement which was diagnosed by necropsy and was probably incidental. The cases reported are too few from which one can draw general conclusions as to the value of parathyroid extract in the treatment of infantile tetany. It is unwise to rely entirely on the extract to the exclusion of other better accepted methods of treatment in infantile tetany until the parathyroid extract treatment is more firmly established on sound clinical bases.—M. B. G.

Relation of calcium and phosphorus in blood of parathyroidectomized dogs. Reed, C. I., R. W. Lackey and J. I. Payte, Proc Soc. Exper. Biol. & Med. **25**: 136-137. 1927.

In normal dogs, the Ca:P ratio in the blood varies from 1.5 to 2. After parathyroidectomy the ratio is reduced until at the first appearance of tetany the ratio is approximately 1.0. The change is due both to decrease in calcium concentration and to increase in inorganic phosphorus concentration.—Author's Abst.

Extirpation of the pineal gland and gonads (Eperimentale Untersuchungen über die Doppelextirpation der Epiphyse und der Keimdrüse). Yohoh, A., Ztschrft. f. d. ges. exper. Med. **55**: 349-370. 1927.

After operations performed on male chicks 30 to 40 days old the following results were noted: Extirpation of the pineal gland

is followed by a noticeably accelerated body growth accompanied by abnormal growth of the testes and a precocious development of the comb. The abnormal growth of the testes may be noticed as soon as 8 days following operation. When both the pineal gland and the testes are removed body growth is noticeably slowed and there is no perceptible growth of the comb. Following the double operation there is atony of the entire body, but this condition does not persist. The pituitary, especially the anterior lobe, becomes twice as large as normal. There are few basophiles, but the acidophile cells of the pituitary increase in number and are hypertrophied. Other internally secreting glands show a slight hypertrophy but all other organs display a growth which parallels the general body growth. The thymus gland in control animals shows regressive changes as growth progresses, but in doubly operated animals the thymus persists for a long time. It is concluded that growth of the body is dependent upon interactions between the pineal gland, the gonads and the pituitary; the pineal gland controlling the functions of the gonads and the pituitary, which in turn condition the growth of the body. The thymus also is in some manner involved.—W. J. A.

Thymic enlargement as a cause of atelectasis. Costello, J. P., Med. Clin. N. A. **11**: 583-590. 1927.

This is a contention that the thymus is a direct cause of certain types of atelectasis in the newborn. The symptomatology and diagnosis are discussed, with the differential diagnosis between atelectasis and similar conditions found in the newborn. The importance of radiology in the diagnosis and treatment of thymic atelectasis is emphasized.—I. B.

The rôle of thymus in chloroform narcosis (Die Rolle des Thymus bei der Chloroform-narkose [Tier Experimente]). Gyorgy, E. and G. Mihalovics, Jahrb. f. Kinderh. **117**: 248. 1927.

To determine if there is a thymic death with chloroform narcosis, white rats were separated into four groups. (1) Chloroform was administered without any further handling. (2) Thymus of a calf was injected in addition. (3) Thymus of rat was injected in addition. (4) Thymus transplanted into the rats in addition to narcosis. Normal non-narcotized rats were used as controls. The authors conclude that the treated animals stood narcosis as well as the controls and that therefore thymic death cannot be considered from a viewpoint of a thymic hyperfunction alone.—M. B. G.

Enlarged thymus—Some observations on the physiology and anatomy of the thymus and thyroid glands. Spohn, H., Trans. Canadian Society for Study of Diseases of Children. Am. J. Dis. Child. **34**: 697. 1927.

The opinion is advanced that there are thymus belts and that these belts correspond to regions in which pathological conditions of the thymus are found. In support of this theory some statistics of comparative incidence between various regions in America are given and note made of the apparent rarity of thymus disorders in Europe. The condition has been found to be fairly frequent, however, by Feer in the neighborhood of Zurich. The observations of Berry are recalled to the effect that in every patient who died of toxic goiter an enlarged thymus was found on post mortem examination. Based upon a study of 120 cases of thymus enlargement with symptoms in which treatment was instituted, the author concludes that in the majority of instances an internal secretion rather than pressure with enlargement is responsible for the symptoms.
—M. B. G.

The early diagnosis and treatment in enlargement of the thymus gland. Sturr, R. P., Arch. Pediat. **44**: 733-741. 1927.

Based on a study of 65 cases of enlarged thymus, the author considers that gland as either a symptom producing or non-symptom producing thymus. The local symptoms due to enlarged thymus are signs of upper respiratory infection, persistent formation of mucus in pharynx and trachea, cough, hoarseness, in crying and coughing, difficult and stertorous breathing, breath holding, cyanosis and attacks of cyanosis. General or toxic symptoms were present in 40 per cent of the cases. All suspicious cases should be given the benefit of x-ray treatment.—M. B. G.

The relation of the thyroid gland to calcium metabolism. Aub, J. C., W. Bauer, M. Ropes and C. Heath, Tr. A. Am. Physicians, **42**: 344-345. 1927.

The relation of the thyroid to carbohydrate, fat and total metabolism has never been established. The serum calcium and phosphorus in myxedema, exophthalmic goiter, and adenoma of the thyroid are normal. The excretion of calcium and phosphorus, however, is not normal. This was established by giving a diet inadequate only in calcium, and by analyzing the excreta for calcium, phosphorus and nitrogen. Thus the minimal rate of calcium metabolism could be established. Thyroid administered to normal controls and to myxedematous patients also causes a definite increase in calcium. It is clearly seen that hyperthyroidism is associated with a very marked increase in calcium excretion. X-rays of the bones of the hand also show a diminished density in patients with exophthalmic goiter, indicating a loss of calcium. Two patients with parathyroid tetany were studied in the course of their treatment with Collip's parathyroid extract and it was clearly demonstrated in both that when thyroid extract was given in addition to constant doses of parathormone, the calcium in the blood and in

the excreta was markedly increased. From these data the following conclusions are justified: (1) The thyroid hormone influences the rate of calcium and phosphorus metabolism in a way similar to its effects on carbohydrate, fat and protein. (2) Hyperthyroidism has an effect similar to the administration of Collip's parathyroid extract in influencing calcium excretion, but it does not raise the level of normal blood calcium. (3) In tetany, due to low-blood calcium, thyroid extract raises the blood-calcium level as well as increases the calcium excretion. In this disease it is an important adjunct in treatment.—I. B.

The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects. 1. A method of studying the reserve or deposit protein with a preliminary report of the results obtained. Boothby, W. M., I. Sandiford, K. Sandiford and J. Slosse, Tr. A. Am. Physicians, **40**: 195-229. 1925.

The effect of thyroxin or dessicated thyroid on the various metabolic functions of the body as evidenced by changes in the respiratory metabolism and the partition products in the urine and blood, are reported on one normal and two myxedematous individuals who throughout the experimental period were eating an accurately known diet. The evidence at present available indicates that thyroxin does not cause a demonstrable change in the true endogenous protein metabolism but does cause a temporary increase in elimination of urea nitrogen, which represents apparently a decrease in the quantity of stored or deposit nitrogen during the period in which equilibrium is being established. The administration of thyroxin or dessicated thyroid to normal or myxedematous subjects on a constant protein intake, to exclude variations in the exogenous protein metabolism, provides a new method for studying the deposit or reserve protein of the body.—I. B.

Relationship of diseased tonsils to goiter. Bram, I., M. J. & Rec. **125**: 442-445. 1927.

Basing his deductions upon the study of a series of 9864 goiter cases, the author urges the adoption of an open-minded attitude in the evaluation of causal relationship in the observation of goiter patients presenting diseased tonsils. The frequency with which infectious foci occur in teeth, nasal passages, sinuses, appendix, gall bladder, and uterine adnexae, must also be borne in mind. We must be conservative in our estimation of the degree of etiological responsibility of infectious foci, since the majority of these patients give a direct statement of psychic trauma as the apparent exciting cause of the syndrome. In several instances in this series the exciting cause of exophthalmic goiter appeared to be tonsillectomy itself; the patient claimed to have been in perfect health until the tonsils were removed, when nervousness, trembling, excitability,

emotionalism, and insomnia appeared, followed by loss in weight, bulging eyes and large neck. Here it is reasonable to assume that tonsillectomy served as a psychic trauma. The same might be said of nasal septum operations, appendectomy, and even ordinary dilatation and curettement of the uterus. Exophthalmic goiter following childbirth is probably not due to parturition **per se**, but to the psychic trauma incident to labor. The following conclusions are drawn: (1) In simple nontoxic goiter it is doubtful whether diseased tonsils play an etiological rôle. Hence, tonsillectomy, without the administration of additional therapeutic measures, usually fails to cure the patient. (2) Diseased tonsils appear to play a minor rôle in the assumption of toxicity (hyperthyroidism) by a previously nontoxic goiter. Tonsillectomy in these cases may result in a degree of amelioration of toxicity but the goiter itself is unaffected. (3) In exophthalmic goiter diseased tonsils may play a **contributory** etiological rôle. The major factors are apparently the predisposing neuropathic makeup of the individual, superimposed upon which a psychic trauma appears to be the usual exciting cause of the affection. Tonsillectomy in exophthalmic goiter with the expectation of curing the disease is usually disappointing; this procedure should be regarded as merely supplementary to more direct therapeutic measures. (4) Despite the frequent disappointments as to results, diseased tonsils should be removed in all goiter cases. Care must be exercised in toxic adenoma and especially in exophthalmic goiter that tonsillectomy be performed at a time when the resultant reaction would appear to be negligible.—Author's Abst.

Hypothyroidism as a cause of intractable constipation. Brown, T. B., Tr. A. Am. Physicians, **41**: 162-167. 1926.

In a number of cases of intractable constipation in middle life, especially in women of obese type, there occurs a subnormal basal metabolic rate. The success of thyroid opotherapy might seem to indicate that these cases are instances of hypothyroidism.—I. B.

Myxedema and Erb's familial muscular dystrophy (Zur Klinik in Pathophysiologie des Myxedems [inbesondere des gutartigen inkompletten Formen]). Curschmann, H., Deutsche. Ztschr. f. Nervenh. **98**: 1-28. 1927.

A case report of a boy of 9 years of age showing an incomplete myxedema and Erb's familial muscular dystrophy. The author believes it to be a coincidental affection of both systems depending upon disturbances of the vegetative centers of the midbrain.

—M. B. G.

Exophthalmic goiter. DeCourcy, J. L., Boston M. & S. J. **197**: 1305-1309. 1928.

A statement of the fundamental factors producing the characteristic signs and symptoms.—J. C. D.

Significance of cardio-vascular methods of investigation (capillary visualization, electrocardiogram, roentgenogram) in the diagnosis of mongolianism and myxedema in children (Die Bedeutung der Kardiovascularen Untersuchungsmethoden [Capillaroskopie, Elektrokardiographie, Rontgenographie] fur die Beurteilung des Mongolismus und des Myxodems beim Kinde). Doxiades, L. and C. Pototzky, Klin. Wchnschr. **6**: 1326-1328. 1927.

Capillary, electrocardiographic and roentgenographic observations were made on 25 mongolian idiots and 15 myxedematous children. In mature full term mongolians the capillary loops are scant but have the form of ripe capillaries, while in prematurely born mongolians they have the form of arched capillaries. The subpapillary and papillary layers are colored light yellow in both premature and full born mongolians. The normal color is rose. In premature mongolians there is a small pulse with thread like formed vessels; there is no change in the rhythm but the blood pressure is 10 to 15 mm.Hg. below the normal. The heart shadow and cardiac dulness is increased in most of the cases. The electrocardiogram in mature mongolian idiots shows a typical indolent vagus heart in mature mongolian idiots and "an infantilism of the cardiovascular system" in prematures. Ip spike is greater than the Ir, the Fp deep and broad. In the myxedematous child is found scant, broad, bluish capillary loops with a grayish white subpapillary layer with wide blue plexuses. The heart is powerful, with a full pulse and normal pressure. The electrocardiogram shows a left heart preponderance, high R spike, low final wave, prolonged stimulation and tense sympathetic heart, as against the indolent vagus heart of the mongolian. The appearance of the capillaries is a gauge for therapy. A case of suspected mongolianism with a subpapillary layer simulating an endocrine picture should be given organotherapy. Arched capillaries denote poor prognosis. If the subpapillary layer does not show any changes in a case of mental delinquency, the prognosis is unfavorable and organotherapy of no avail. The results of treatment may also be checked up by observations of the cardiovascular system. The authors use thyroid and anterior pituitary extract alternately.—M. B. G.

Results of thyroidectomy for hyperthyroidism as indicated by examination a year or more following operation. Elliott, C. A., Tr. A. Am. Physicians, **41**: 91-99. 1926.

This series of 74 patients operated upon is divided into two groups: One group was thyroidectomized more than a year previously and the other from 6 to 12 months prior to examination. **No**

discrimination was made between toxic adenoma and exophthalmic goiter. The author states that subtotal thyroidectomy arrested hyperthyroidism in 71 out of the 74 cases studied. Three of the 71 showed evidences of myxedema, which was controlled by thyroid extract. Three cases of the 74 remained slightly hyperthyroid. Permanent tissue damage was noted in 49 of the 74 cases 6 months to 6 years after operation. In 37 cases residual damage was present without symptoms, while in 12 patients partial disability was present.—I. B.

Long-standing hyperthyroidism with spontaneous subsidence. Eshleman, C. L., Med. Clin. N. A. **9**: 1103-1107. 1926.

This is a report of a case in a colored woman 57 years of age who had been under observation for marked exophthalmic goiter for 14 years. The improvement noted during this period of time is regarded as spontaneous, since the author cannot associate it with any treatment. The patient, though she recovered spontaneously from the primary condition, is now regarded as a chronic cardiac case, able to carry on only a part of her accustomed duties. The author concludes that while incipient cases may become well spontaneously, this is rare in severe Graves' disease, hence this case is worthy of note. Severe cardiac damage is to be expected under the circumstances.—I. B.

Experiments in myxedema in childhood (Versuche beim Myxedem im Kindesalter). Geldrich, J., Jahrbuch f. Kinderh. **117**: 247. 1927.

The influence of thyroxin on the basal metabolic rate was followed in a 14-year-old myxedematous girl who originally showed a B. M. R. of minus 25 per cent as against that of a normal girl. Thyroxin, 0.02 mgm. twice a day, was administered for 9 days. In the myxedematous girl, the rate rose 25 per cent on the first day following the administration, 50 per cent on the next day, and finally up to 70 per cent on the day after the suspension of treatment. The rate on the 18th day after the treatment had been discontinued was still 20 per cent increased. The initial rate was not reached even in one and a half months after cessation of treatment. The rate in the normal girl was increased 14 per cent, with a drop to normal by the 14th day. The author concludes that a hypothyroid child is much more sensitive to thyroxin than a normal one.
—M. B. G.

The management of goiter patients with congestive heart-failure. Grant, S. B. Med. Clin. N. A. **11**: 569-581. 1927.

Congestive heart failure in goiter patients responds to treatment far more satisfactorily than is the case in other types of cardiac disease. Especially is this true following successful thyroidec-

tomy in patients suffering with toxic adenoma. Patients of this type should undergo a period of preoperative attention in which the internist, surgeon and laboratory clinician should share the responsibility.—I. B.

The effect of acetyl thyroxin on the teeth of newborn rats. Hoskins, Margaret M., Proc. Soc. Exper. Biol. & Med. **25**: 55-57. 1927.

Subcutaneous injection of acetyl thyroxin into newborn white rats causes precocious development and eruption of the incisor teeth, which penetrate the epithelium three to five days before the teeth of the control animals erupt. The effect on these teeth is comparable to that produced on other parts of the body. The formation of enamel does not show a greater degree of acceleration than any other process of tooth formation. The molars of injected rats are not affected by the acetyl thyroxin.—Author's Abst.

Injuries to the recurrent laryngeal nerve in operations of the thyroid gland. Kelly, T. H., and V. Wippern, Illinois M. J. **51**: 307-311. 1927.

When compared to the great number of thyroidectomies performed annually, injury to the recurrent laryngeal nerve is uncommon. The surgeon should examine the larynx preoperatively to determine the condition of the vocal cords, and again before the patient leaves the hospital. Unless promptly treated, the resulting dyspnea from bilateral paralysis may be fatal. However, in the case of unilateral paralysis producing hoarseness or bilateral paralysis with complete aphonia, most authorities report clinical cures within from three months to a year. Injury to the recurrent laryngeal nerve may be avoided by careful technic and by leaving a portion of the posterior part of each lobe.—I. B.

The geographical distribution of goiter. Kerr, W. J., Tr. A. Am. Physicians, **42**: 326-329. 1927.

As conditions in remote and uncivilized districts become known, it is apparent that no country is entirely free from goiter. The known endemic foci are in Switzerland, India, France, Italy, Germany, Russia, China, Australia, New Zealand, Africa, South America and North America. Around the Great Lakes and in the Pacific Northwest we have large areas of moderate incidence, with smaller centers where almost the whole population is affected. The author had an opportunity during the World War to study the incidence of goiter in a region covering approximately one-third of the total area of the United States, comprising the states of Minnesota, the two Dakotas, Montana, Wyoming, Utah, Idaho, Washington, Oregon, Nevada and California. The examinations were made on drafted men coming to Camp Lewis, Washington, during the second draft. Examinations were made on over 21,000 recruits at the same time of

the year, the ages ranging from 21 to 31 years. The draft quotas were known and, in general, were based upon population. The incidence in the group from each county was easily determined, which served as an index of the degree of endemicity in this large section of the country. In these examinations the author was assisted by Thomas Addis, of San Francisco, and Karl Moran, of Portland. The figures of the War Department of the United States Army suggest that exophthalmic goiter is most prevalent in regions of high incidence of endemic goiter. This is contrary to the generally accepted opinion, that the frequency of the one varies inversely with the frequency of the other. Kerr believes that the Army statistics are subject to error, in view of the general lack of knowledge of the classification of goiter among the medical profession. Many cases of large toxic goiter without eye signs were probably classified as exophthalmic goiter. There is a great variation in the incidence of endemic goiter along the sea-coast, and in certain instances it is much higher than in inland regions.—I. B.

Exophthalmic goiter and the involuntary nervous system, XVI. The influence of subtotal thyroidectomy with and without compound solution of iodine on the course of the disease. Kessel, L., and H. T. Hyman, Arch. Int. Med. **40**: 623-636. 1927.

The authors' purpose is to furnish data whereby a comparison can be made between the course of exophthalmic goiter without the institution of specific therapeutic measures, and the course when subtotal thyroidectomy and the iodides are employed. A study of 129 patients was made. Of these, 69 were not submitted to operation, due to factors beyond the control of the observers, while 60 underwent subtotal thyroidectomy. Of the latter, 31 received no preoperative iodine treatment. The immediate postoperative mortality was 11 per cent, while the total mortality of the entire group of the 129 patients studied was 19 per cent. The average time of observation of these patients was approximately 24 months. The earliest case was under observation four years and the most recent 9 months. Of those not operated upon, 28 improved spontaneously. Three of the operative deaths were from the group of 31 patients who did not receive iodine solution, and 4 were from the group of 29 who were prepared with iodine. On discharge, 33 per cent of the patients operated upon declared themselves to be symptom-free for the first two years of observation. At one time or another 15 patients, or 25 per cent, had a marked exacerbation of symptoms. The remainder were benefited in such degree as to be capable of performing most of their social or economic functions. Only four patients of the group operated upon experienced a perceptible decrease in the degree of exophthalmos; in the remainder no improvement was noted, while in 11 there was a perceptible increase. The pulse rate, because of its persistent lability, could not be published

with accuracy; it is believed, however, that a certain amount of tachycardia persists in all.—I. B.

Thyroid dysfunction as a cause of fever. Lee, R. I., Med. Clin. N. A. **10**: 1353-1355. 1927.

The case described occurred in a woman of 41, whose chief complaints were an afternoon rise in temperature (99 deegrees to 100 degrees F.), indefinite digestive disorders and occasional cough. A diagnosis of phthisis was made on the discovery of significant signs in the apex of one lung. Despite competent treatment and a prolonged rest cure, the rise in temperature persisted with the curious low pulse rate of 50 to 60. A basal metabolism study revealed an average of minus 20 per cent. Administration of small doses of thyroid extract effected a disappearance of the fever and an elevation of the B. M. R. to normal. The experiment of omitting thyroid extract treatment resulted in the return of the fever.—I. B.

Relation of endemic goiter to the iodine content of soil and drinking water. McCarrison, R., C. Newcomb, B. Viswanath, and R. V. Norris. Indian J. M. Research, **15**: 207-246. 1927.

The investigations relate solely to the classic or adeno-parenchymatous type of endemic goiter occurring in the Alps and other mountainous regions in association with cretinism, deaf-mutism, and idiocy, and is the type which McCarrison has studied in Chitral, Gilgit, and other parts of Himalayan India. It is, too, the type of goiter occurring in animals living in captivity under unhygienic conditions of life, as in artificially-bred trout confined in tanks. It is, McCarrison believes, the same disease which he produced experimentally in man by the administration of **unboiled** suspended matter present in goiter-producing waters, and in rats and goats by the administration of cultures of fecal bacteria. The authors arrive at the following conclusions: In sea-coast, sub-montane and montane localities (ex-Himalayan India), where endemic goiter is unknown, the iodine content of the soil may be low, moderate or high. Hence the freedom of these localities from goiter is related to conditions other than the iodine content in their soils. The richness of a soil in iodine does not preclude the presence of thyroid swellings (mostly so-called "incipient goiters") in 27.7 per cent of girls and in 11.8 per cent of boys living at an altitude of 6,000 feet above sea-level and in a place where endemic goiter is conspicuous by its absence in the general population. Investigation has proved no evidence that in Himalayan Indian the incidence of endemic goiter is in inverse ratio to the iodine content of the soil. In the heart of the endemic zone, as well as in the Himalayan foothills, two places adjacent to one another may have approximately the same amount of iodine in their soils, yet goiter be endemic in the one and not in the other; or, the soils of two villages situated on the same water supply

may be equally poor in iodine, yet goiter be four times as prevalent in the one as in the other. The water supply of a given place may contain an appreciable amount of iodine, and yet goiter be endemic therein; the water supply of another may contain less iodine and yet goiter may not be endemic therein. Drinking water containing 300 parts of iodine per 100 billion parts of water has not prevented endemic goiter in the presence of a high degree of bacteriological impurity of the water; nor has the consumption of a drinking water containing 1,200 parts of iodine per 100 billion parts of water prevented the development, under experimental conditions, of this disease in young men who consumed large amounts of the suspended matter removed by filtration from a grossly-polluted goiter-producing water. The substitution of a bacteriologically pure for a bacteriological impure water has caused the rapid disappearance of the endemic, although the new water supply contained less iodine than the old. The bacteriological impurity of the water supply was the essential cause of the disease. Although the iodine content of the soil and water is not in itself the essential cause of this type of endemic goiter in Himalayan Indian, yet the disease is less likely to arise under experimental conditions in iodine-rich localities in Southern India than in iodine-poor localities in Himalayan India. The essential cause of this type of endemic goiter in Himalayan India is the unhygienic conditions of life of the people. Among these conditions bacteriological impurity of their drinking water and their surroundings is the chief. A deficiency of iodine relative to these conditions of life is favorable to the development of the disease.

—I. B.

The experimental production of a new type of goiter unrelated in its origin to iodine. McCarrison, R., Indian J. M. Research, **15**: 247-263. 1927.

The author reports the experimental production in rats of a new type of goiter which is unrelated in its origin to iodine deficiency. It was produced by the prolonged feeding of a diet containing more than 60 per cent white flour or of vitamin-poor carbohydrates, 20 per cent or less protein with fats and inorganic salts (including iodine) in adequate amounts, but no fruits or green vegetables. The author distinguishes this type of goiter from the well-known endemic goiters. This new type of goiter is characterized mainly by marked "secretory hypertrophy," with little or no increase in the size of the gland. The progression of the secretory hypertrophy leads eventually to exhaustion of the secretory cells and ultimately to fibrous tissue replacement. McCarrison believes it likely that this type of goiter occurs sporadically among white-flour-eating peoples, and that in its presence that Graves' Disease may be precipitated by such influences as pregnancy and lactation, fright and mental strain. This type of goiter is not preventable by iodine, but by a well-balanced vitamin-rich diet.—S. Shapiro.

Spontaneous decrease of goiter in Spain. Marañon, G., Arch. de med., cir. y espec. **27**: 549. 1927. Abst. J. Am. M. Ass. **90**: 245.

In Spain, as well as in other countries, goiter and creatinism have decreased greatly of late without any scientific attack against the disease. In some districts, where practically everybody had goiter fifty years ago, barely four or five cases remain at present. Goiter seems to subside as living conditions improve. In the most typical Spanish focus, Las Hurdes, the communities worst affected are those at the greatest altitude, i. e., the most isolated. Food deficiency and endocrine gland disturbances act on the two great organic processes, growth and development. It seems as if in goiter cases the glands of internal secretion lack some substance necessary to the manufacture of their hormones. As the alimentary deficiency is apparently related to animal proteins, an analogy to pellagra is suggested. Other factors may intervene, but the only invariable element is undernourishment and poverty.

An exophthalmic goiter of peculiar type. Mix, C. L., Med. Clin. N. A. **9**: 1255-1260. 1926.

The case described occurred in a woman 67 years old. Tachycardia was absent, nor was there any tangible thyroid enlargement. Exophthalmos, loss of 83 pounds in weight, and other typical symptoms of the disease were present, with a basal metabolic rate of plus 97 per cent.—I. B.

Case of hyperthyroidism simulating primary heart disease. Priest, W. S., Med. Clin. N. A. **9**: 1337-1351. 1926.

The author calls attention to the importance of differentiating cases of thyroid hyperfunction without exophthalmos and without obvious goiter from those of primary heart disease. Basal metabolism determinations should be made in all cases of alleged heart disease not responding to treatment with a view to the discovery of possible thyroid toxicity.—I. B.

Hyperthyroidism and its relation to benign tumors of the thyroid gland. Reinhoff, W. F., South. M. J. **20**: 901-906. 1927.

The thyroid is in a state of flux as shown by the histological changes brought about by feeding iodine in exophthalmic goiter. All patients with hyperthyroidism show histological changes. The term toxic adenoma is not justified, for the gross condition of the thyroid is the result of the balance between hypertrophy, hyperplasia, and involution, which may have taken place in the gland recently or over a long period.—J. C. D.

Action of ergotomine on the blood in Basedow's disease and in animals [Die Wirkung von Ergotamin (Stoll) beim basedow und in

tierversuch auf die Blutzusammensetzung]. Rothschild, F., and M. Jacobsohn, Ztschr. f. kin. Med. **105**: 406-409. 1927.

Briefly the authors have shown that upon using 0.5 mgm. ergotamine-tartrate on patients with Basedow's disease, a vagus effect on the blood predominated; this expressed itself through a drop of blood sugar, cholesterin and calcium and rise of non-protein nitrogen and potassium. Organic and inorganic phosphorus fell as when adrenalin and thyroid extract are used. In animals, the sympathetic effect predominated: blood sugar, phosphorus and calcium rose, potassium and cholesterin fell, and non-protein nitrogen rose slightly.
—H. J. J.

Mongolian maldevelopment, upon the basis of clinical, statistical and anatomical investigations (Beitrage zur Kenntnis der Mongoloiden Missbilddung auf Grund klinischen, statistischen und anatomischen Untersuchungen). Van de Scheer, W. M., Abh. a. d. Neurol. Path. Psychol. und ihren Grenzgeb. **41**: 1-162. 1927.

Mongoloid form of idiocy belongs to the class of congenital malformations. The congenital anomaly can be carried back and attributed to a narrow amniotic sac, which exerts its influence during the sixth or seventh week of embryonic life. The disturbance in development of the amnion results from a faulty implantation of the ovum in an abnormal endometrium. On the basis of a local condition of the endometrium, the author advances the above hypothesis, especially since there is no evidence in the history of the parents, emotional states of the parents or any other factor which is responsible for the condition. In favor of it is the advanced age of the mother in many instances, the mongolian is the last born, history of still births and miscarriages and the absence of mental defects in other members of the family except perhaps the occurrence of another mongolian idiot.—M. B. G.

Influence of the thyroid gland of selacians and teleosts on the metamorphosis of frog tadpoles [influence de la gland thyroïde des sélaciens (Scyllium canicula Cuv. et Sc. stellare Gthr.) et des téléostéens (Cyprinus carpio L.) sur la métamorphose des têtards des anoures (Rana temporaria L.)]. Sembrat, K., Compt. rend. Soc. de biol. **97**: 1508-1510. 1927.

Transplants materially hastened metamorphosis.—J. C. D.

Adolescent thyroid and goiter in Steiermark (Uber Jugenschildruse und Kropf in Steiermark). Orator, V., and E. Walchshoper, Deutsche Ztschr. f. Chir. **201**: 310-319. 1927.

On the basis of operations and necropsy findings in Steiermark, where goiter is endemic, the authors report the following classifications: In early infancy the thyroid shows definite lobular markings,

the lobules being made up exclusively of solid colloid-free parenchyma (new-born type). From the fourth year on is found the central vesicle type with distinct lobar and lobular structure, but in the center of each lobule can be seen an empty vesicular structure surrounded by a solid colloid-free parenchyma. This type with the emptied vesicle is spoken of as the "open and transitional type" as long as the vesicle is empty, but if it becomes filled it is then known as the normal thyroid of childhood. The normal adolescent type found after the age of 16 years shows small follicles filled with colloid arranged in pronounced strata about a large central vesicle.

—M. B. G.

The fate and characteristics of mongolian children (Schicksale und charackteristik mongoloider Kinder). Steinen, R. v. d., Monatsschr. f. Kinderh. **35**: 495-504. 1927.

Of the 73 children whose follow-up history was obtainable, 46 had died, the majority of either lobar or broncho-pneumonia. Only 4.1 per cent reached the age of 20 years. Congenital heart conditions were present in 14 children and generally caused death before the end of the third year. Practically all of the children in the series showed a tendency to upper respiratory infections. None of the children were proficient in any occupation; the memory was fair, but all were deficient in arithmetic. They were able to perform manual work. Of those who survived, three-tenths showed some maldevelopment, while of those who died, eight-tenths.—M. B. G.

The relationship of endemic goiter to tuberculosis (Uber den Endemischen Kropf und seine Beziehungen zum Tuberkulos). Susani, O., Mitt. a. d. Grenzgeb. d. Med. u. Chir. **40**: 146-153. 1927.

Tuberculosis in the active form was found in all of the cases (48) of parenchymatous goitre seen at the out-patient department of the Vienna Surgical Clinic. The type was either of the inflammatory primary complex or of the proliferating primary complex. Iodosterine did not produce any favorable results. The author feels that this type of goiter has tuberculosis as its chief etiological factor.

—M. B. G.

Indications for thyroidectomy. de Takats, G., Illinois M. J. **51**: 306-307. 1927.

The author advises thyroidectomy in (a) large diffuse colloid goiters in individuals past 21 years of age in whom medical treatment has been of no avail, and in simple large adenoma with or without cystic degeneration; (b) goiters producing pressure symptoms, as well as all substernal goiters; (c) functional hypothyroid cases with adenoma and hyperthyroid cases in which the basal metabolic rate is above plus 15 per cent.—I. B.